

*Welcome to the  
FDA CDRH Public Workshop:*

# **Point of Care PT/INR Devices for Monitoring Warfarin Therapy**

*Please set computers, cell phones,  
and Blackberries on silent mode,  
and answer all calls in the hallway*

**Docket No. FDA-2015-N-4462**



# Welcome to our Two Audiences

- **In the room and on the web**
- If you cannot be here in person, or if you have additional comments later, please submit your comments through the docket at <http://www.regulations.gov>: **FDA-2015-N-4462**
- Comment period closes **April 18, 2016**.
- Tweet @ **#PTINRFDA**
- Send questions to: **PTINRworkshop@fda.hhs.gov**

# Housekeeping items

- Please set computers, cell phones, and Blackberries on silent mode, and answer all calls in the hallway
- Webcast Link: <https://collaboration.fda.gov/ptinr/>
- Food and beverages will be available for purchase by workshop participants at the Sodexo kiosk in the registration lobby
- Wi-Fi can be accessed using the network titled “**FDA-Public**” in the Great Room area using: *publicaccess*
- Links to the meeting transcript and the archived webcast will be posted to the workshop registration webpage approximately 6-8 weeks after the meeting
- Please use the microphones for questions/comments

# Acknowledgements

## **PT/INR Workshop Committee**

- Lea Carrington, MBA, MS, MT(ASCP)
- Yvonne Doswell, DHSc, MPH, MBA
- Rachel Goehe, PhD
- Chester Li, PhD
- Kennita Riddick, MS
- Niquiche Sangster-Guity, PhD
- Takeesha Taylor-Bell, H(ASCP)
- Cheng Zhang, PhD, RAC

## **DIHD**

- Kelly Oliner, PhD
- Rong Rong, MD, PhD



# ***Opening Remarks***

**Alberto Gutierrez, PhD**

Office Director

Office of In Vitro Diagnostics and Radiological Health

CDRH/FDA

## ***Workshop Overview***

**Lea Carrington, MBA, MS, MT(ASCP)**

Division Director

Division of Immunology and Hematology Devices

OIR/CDRH/FDA

# **Session 1**

## **Clinician and Patient Perspectives**

**Moderator**  
**Rachel Goehe, PhD**

*Scientific Reviewer*  
*Hematology Branch*  
*Division of Immunology and Hematology Devices*  
*OIR/CDRH/FDA*

# Overview of Warfarin Therapy

March 18th, 2016

**Rong Rong, MD, PhD**

Medical Officer

Division of Immunology and Hematology Devices  
Office of *In Vitro* Diagnostics and Radiological Health  
Center for Devices and Radiological Health

**Docket No. FDA-2015-N-4462**



# Discovery of Warfarin

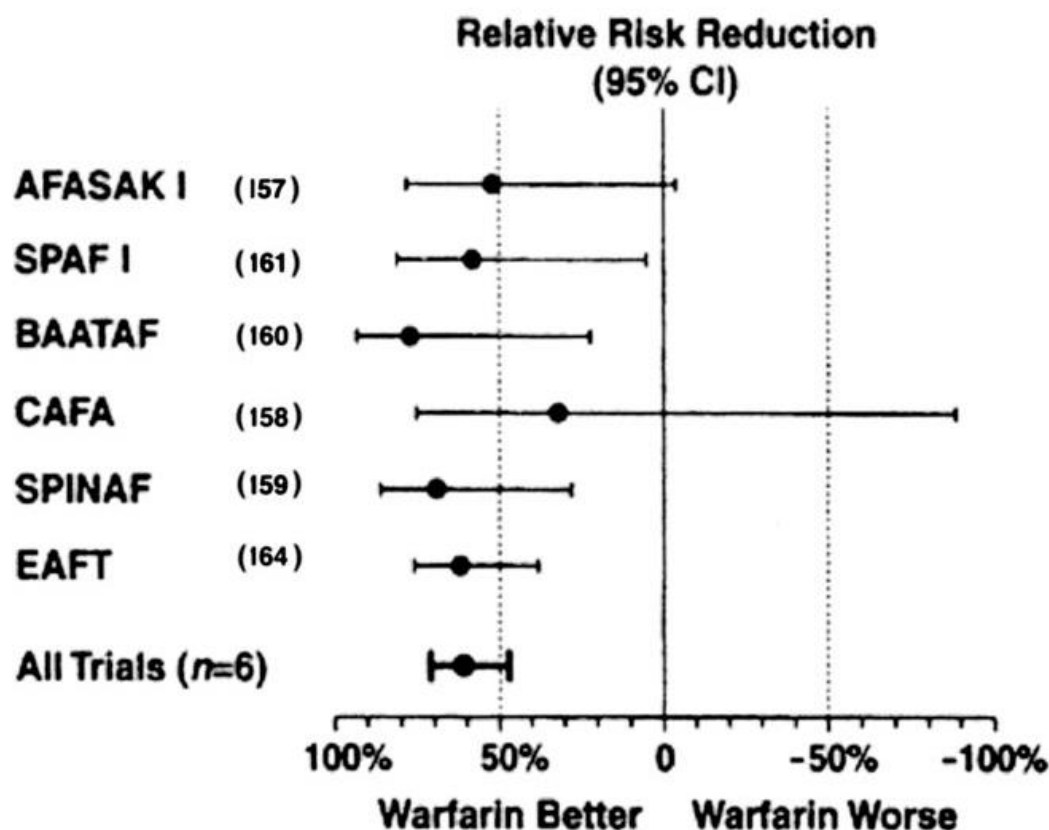
- **1920s: Sweet clover disease**
- **1940s: Warfarin**
  - Dr. Karl Link's laboratory
  - Wisconsin Alumni Research Eoundation + "-arin"
  - Rodenticide
- **1954: Initial U.S approval for human use**
- **1960: First randomized clinical trial**
  - Barritt & Jordan
  - 73 patients with PE
  - Untreated: 5 deaths from PE
  - Treated: 0 deaths from PE



# Clinical Indications for Warfarin Therapy

- **Prevention of stroke for atrial fibrillation**
- **Prevention of thrombosis and embolism for valvular heart disease**
- **Prevention and treatment of deep vein thrombosis**

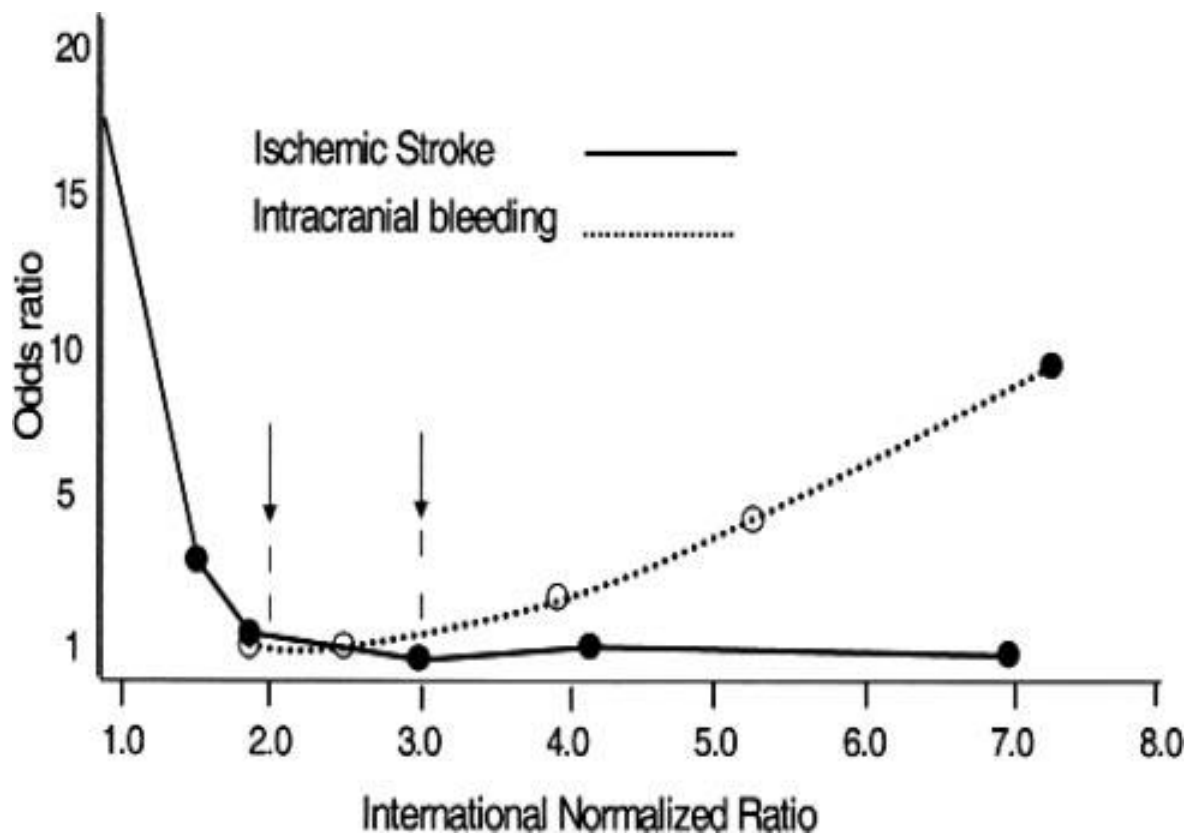
# Adjusted-dose Warfarin Prevents Stroke in Patients with Atrial Fibrillation



Fuster et al., Eur Heart J. 2006 Aug;27(16):1979-2030.



# Balance Between Prevention of Ischemic Stroke and Avoidance of Hemorrhage

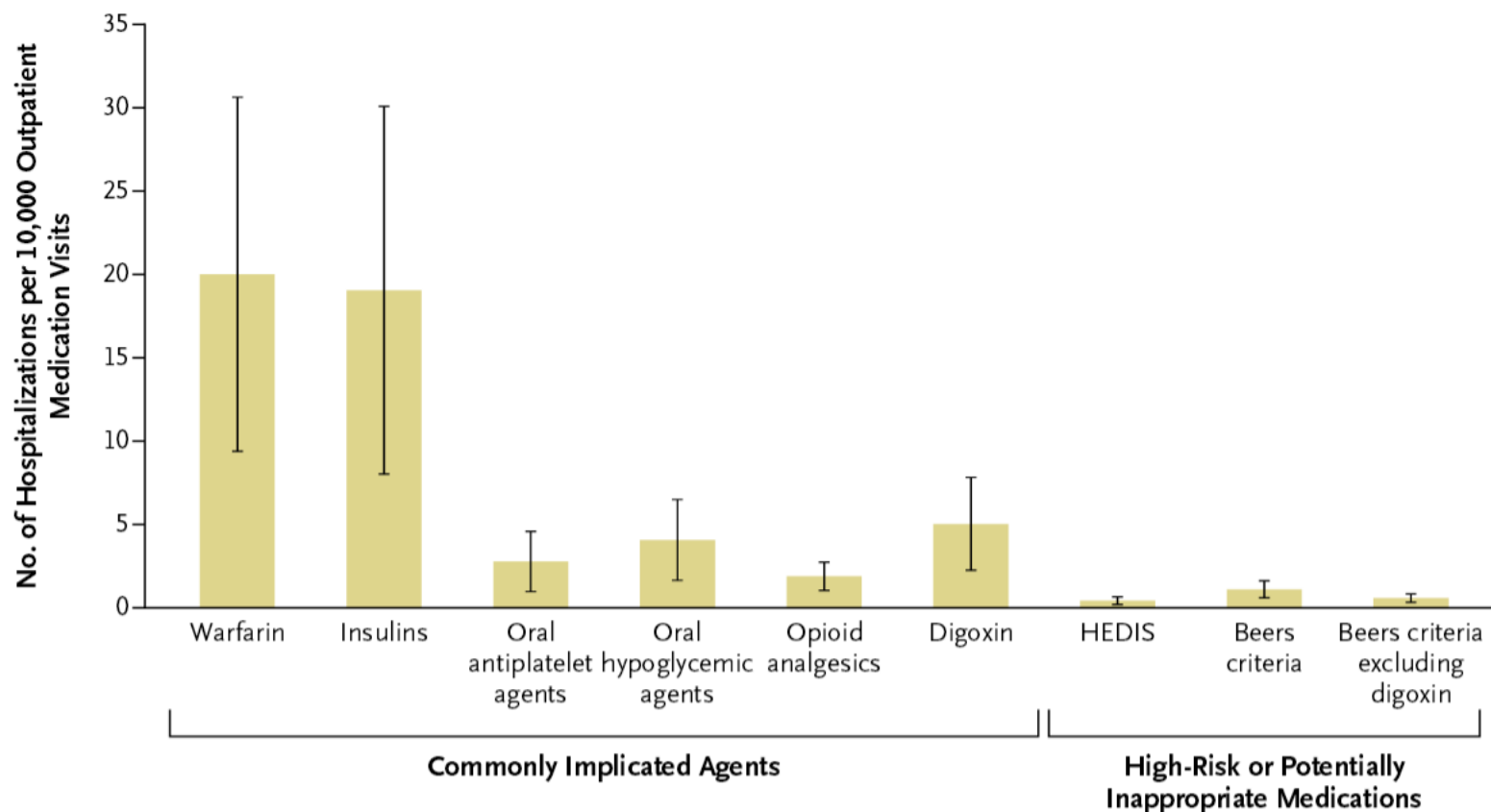


*Fuster et al., Eur Heart J. 2006 Aug;27(16):1979-2030.*

# American College of Chest Physicians Guideline

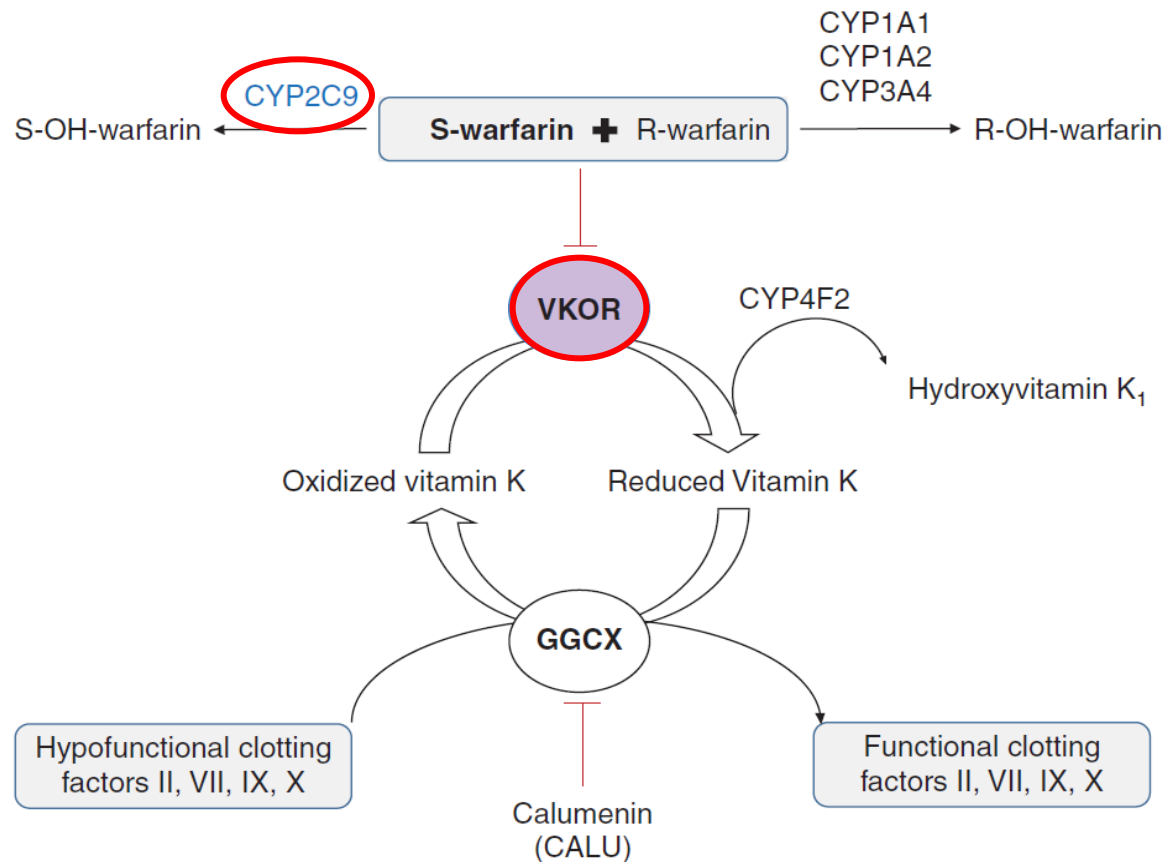
- **Target INR range**
  - Most of the indications: 2.0-3.0
  - Mechanical prosthetic mitral valves: 2.5-3.5
- **Monitor INR every 4 weeks**
  - Every 12 weeks in stable patients
  - Above target range: Increase frequency of monitoring
- **Supratherapeutic INR in patients without significant bleeding**
  - Greater than target range, but <4.5: Decrease/hold dosage or may continue current dosage if INR is 0.5 or less above therapeutic range in a previously stable patient
  - 4.5-10: Hold next one or two doses
  - >10: Hold warfarin and administer Vit K.

# Warfarin-associated Adverse Event in Older U.S. Adults



Budnitz et al., *N Engl J Med.* 2011 Nov 24;365(21):2002-12.

# Warfarin Metabolism & Mechanism of Action



Johnson JA et al., Clin Pharmacol Ther. 2011 Oct;90(4):625-9.

# Multiple Factors Affect Warfarin Response

- **Factors associated with interindividual variability**
  - Pharmacogenetics
  - Ethnicity
- **Factors associated with intraindividual variability**
  - Drug & herbal medications
  - Vitamin K-rich Food
  - Disease state
  - Others

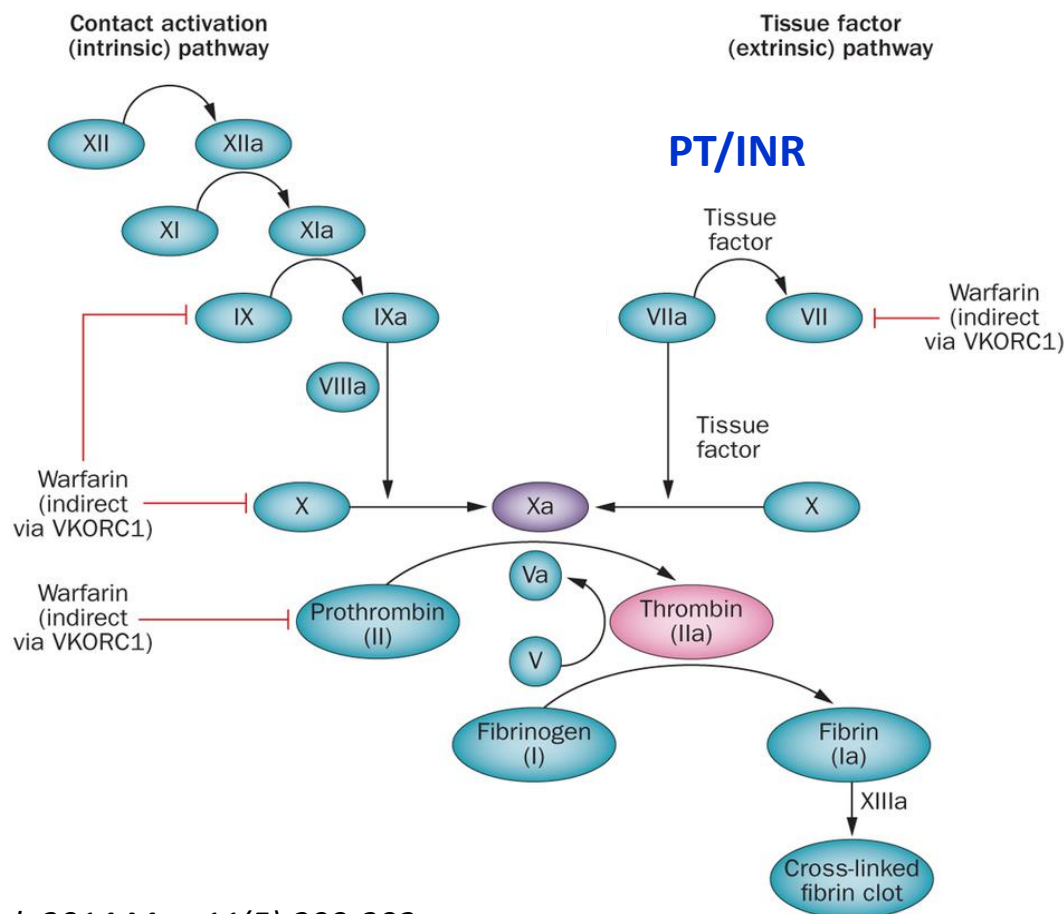
# Drug, Herbal and Food Interaction

- **Drugs**
  - A large number of drugs interact with warfarin
  - Anticoagulants, antiplatelet agents, NSAIDs & serotonin reuptake inhibitors
  - Inhibitors / inducers of CYP450
- **Herbs**
  - Garlic & ginkgo (additive to warfarin effect)
  - Co-enzyme Q<sub>10</sub>, St. John's wort & ginseng (decrease warfarin effect)
  - CYP450 interactions
- **Foods**
  - Green leafy vegetables
  - Alcohol, green tea & cranberry juice

# Many Diseases Affect Warfarin Response

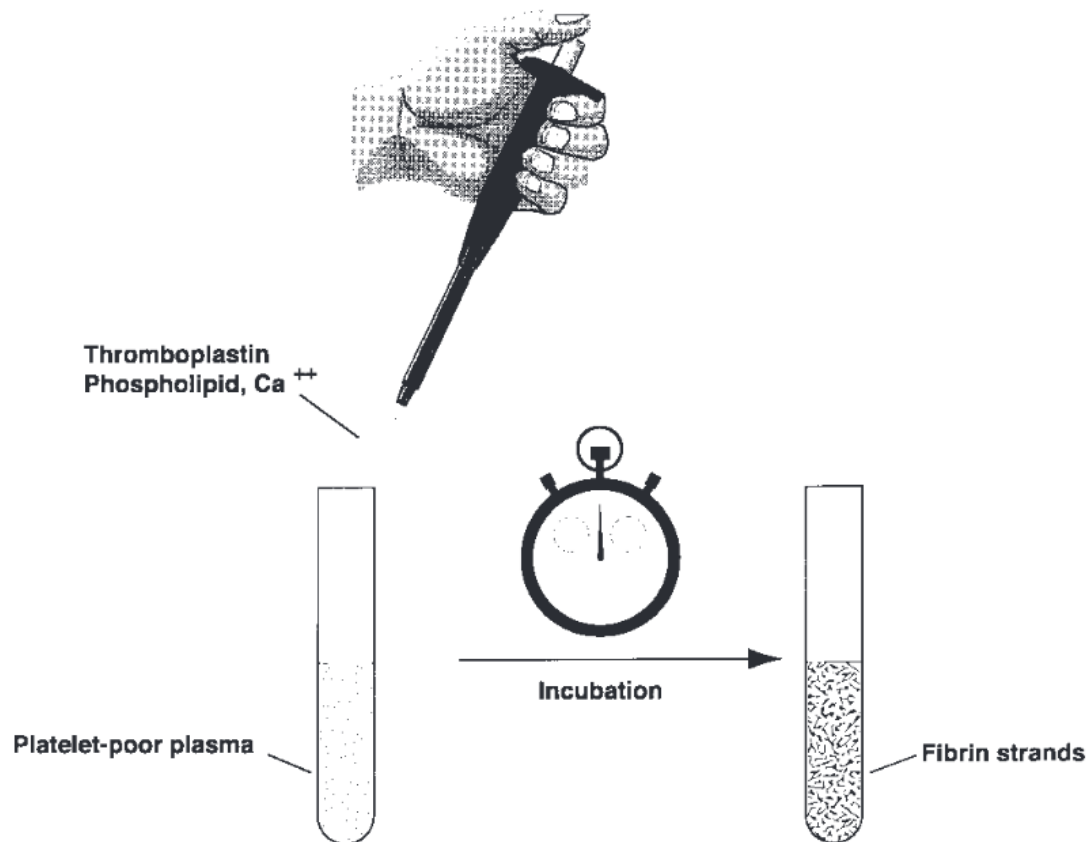
- **Diseases associated with increased response**
  - Liver disease
  - Hyperthyroidism
  - Chronic kidney disease
  - Heart failure
  - Fever
  - Diarrhea
- **Diseases associated with decreased response**
  - Hypothyroidism
  - Obesity

# PT/INR Values are Utilized to Evaluate the Extrinsic and the Common Coagulation Pathway





# Prothrombin Time (PT) Measures Clotting in Response to Exposure to Thromboplastin



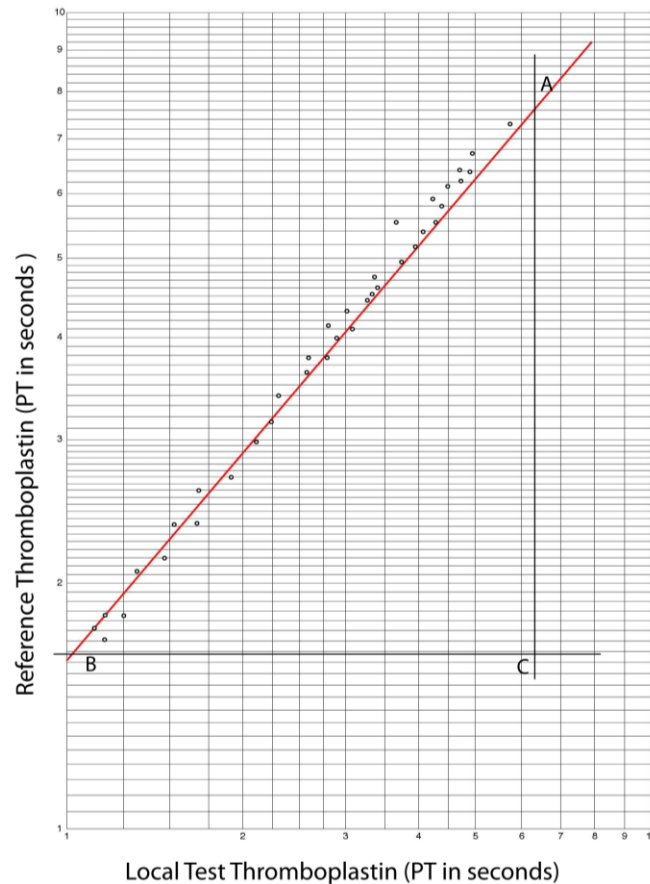
# The INR Calculation Standardized the PT Measurement

- **Variable sensitivity of thromboplastin reagents**
- **INR calculation**

$$\text{INR} = \left( \frac{\text{Patient PT}}{\text{Mean Normal PT}} \right)^{\text{ISI}}$$

- **Assignment of ISI value**
  - Compare test reagent to International Reference Preparation
- **Establishment of MNPT**
  - Geometric mean of PT from 20 normal samples

# Calibration of Thromboplastin & Calculation of ISI



$$ISI_{\text{test}} = ISI_{\text{reference}} \times \text{slope}$$

# Variables Affecting PT/INR Results

- **Pre-analytic**
  - Patient factors
  - Specimen collection, preparation & Storage
  - Type and concentration of anticoagulant
- **Analytic**
  - Type and sensitivity of thromboplastin
  - Assay conditions
  - ISI calibration
  - Instrumentation effects
  - Heparin, lupus anticoagulants & other substances
- **Post-analytic**
  - INR calculation
  - Result reporting

## Comparison between POC and Laboratory Coagulation Analyzer

	POC	Lab coagulation analyzer
<b>Specimen type</b>	Capillary whole blood	Platelet-poor plasma
<b>Neutralization of excess citrate</b>	No	Yes
<b>Thromboplastin</b>	Most use human recombinant	Different types
<b>Thrombin substrate</b>	Some use synthetic thrombin substrates	Fibrinogen
<b>Method of endpoint detection</b>	More varieties	Photo-optical, mechanical etc.
<b>ISI &amp; MNPT</b>	Manufacturer determined	Local calibration
<b>Patient self-testing/self management</b>	Yes	No
<b>Proficiency testing</b>	Not established for home use	required

## CLSI POCT14-A

**“INR system is very useful but imperfect, and clinically important discrepancies of INR are often observed among different laboratory-based PT test system as well as point of care test systems.”**

**“The likelihood of observing clinically important system differences increases as INR rises above 3.0.”**

## An Illustrative Case from a Submitted Medical Device Report

- Patient had a cerebrovascular accident and was treated with warfarin
- Abnormal bruising and ecchymosis
- POC test performed by home health nurse showed a result of **2.4**
- Heart rate was 109; blood pressure was 100/78
- The patient was later sent to the emergency room due to the abnormal bruising and had emesis of blood.
- Laboratory testing: Lab INR = **9.1**; hgb = 6.4; hct = 19.7.
- Treatment included vitamin k and fresh frozen plasma.
- Patient died of gastrointestinal bleed.
- Home health nurse has been using the POC INR device for "several years" and is well trained on the device.

# Summary

- **Warfarin can effectively prevents serious thromboembolic events**
- **Warfarin can cause major or fatal bleeding**
- **Narrow therapeutic range**
- **Significant intra-individual variability**
- **Frequent INR monitoring is required for safe & effective use**
- **Inaccuracy in INR measurement can result in serious consequences**



# Thank you

# Point-of-Care INR Testing: A Clinician's Perspective

Michael B Streiff, MD FACP

Associate Professor of Medicine and Pathology

Medical Director, Johns Hopkins Anticoagulation Service

Chairman, VTE Guideline Committee ,National Comprehensive  
Cancer Network

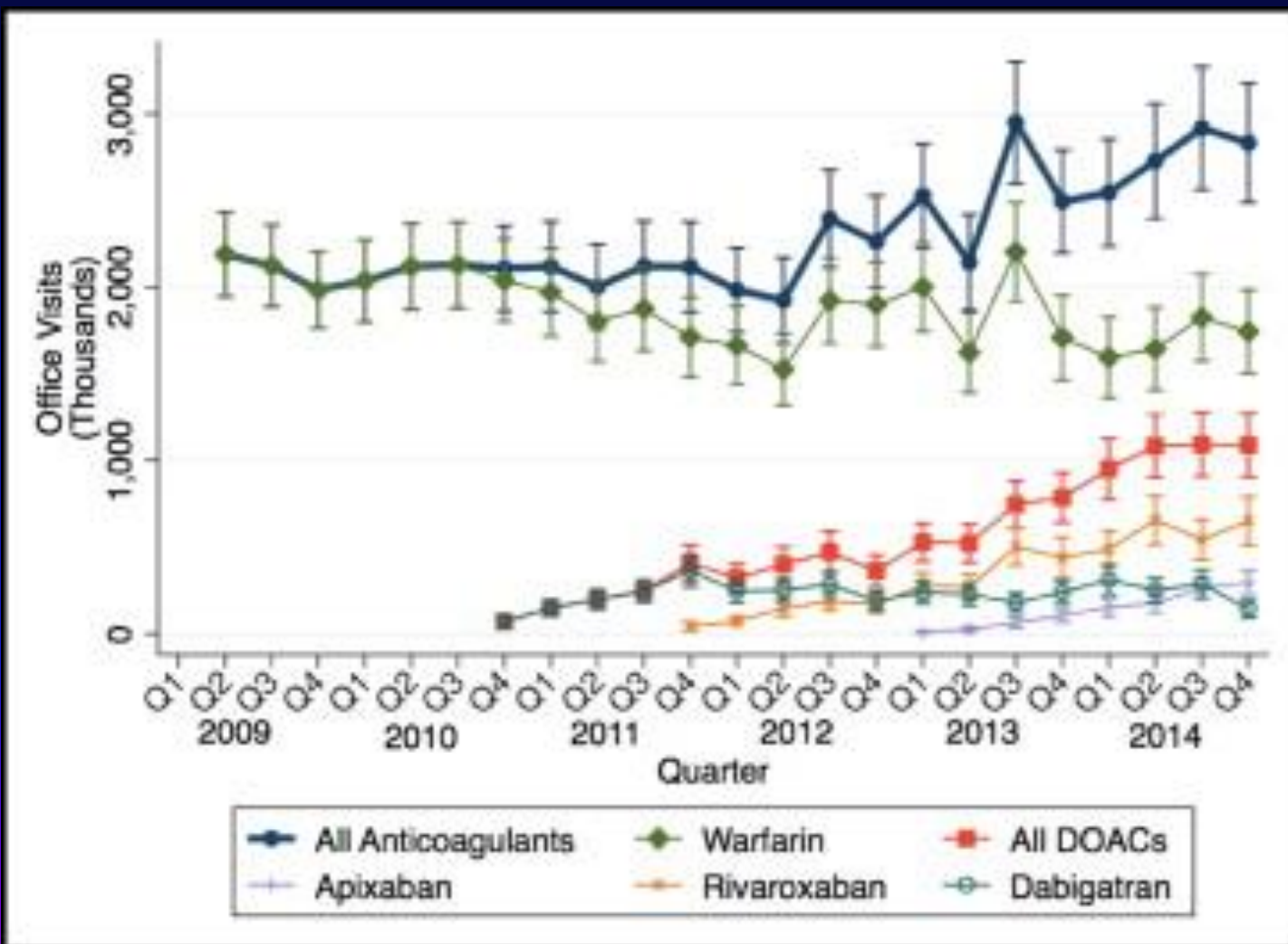
# Disclosures- Michael Streiff, MD

- Advisory Board-Clinical Trials
  - Bio2 Medical
  - Janssen HealthCare
- Educational Grants
  - Covidien
- Research support
  - Daiichi-Sankyo
  - Janssen Healthcare
  - PCORI
  - Portola

# Is Warfarin dead?

1. Increasing patient population who will need anticoagulation
  - Increasing prevalence of venous thromboembolism and atrial fibrillation
2. Direct oral anticoagulants are not suited for everyone
  - Randomized controlled trials excluded patients with liver and kidney disease and coagulation disorders

# National Trends in Oral Anticoagulant Use



# Point-of-Care INR monitoring

## Advantages

- Rapid turnaround time
- More frequent INR testing
- Out-of-hospital INR testing
- Patient self testing
- Patient self management

## Disadvantages

- Lupus inhibitors affect results
- Hematocrit affects results
- Fibrinogen affects results
- Anticoagulants affect results

# Point-of-Care INR Testing Modes

- Outpatient Clinic POC INR testing
- Patient Self Testing
- Patient Self Management

# Patient Self Testing leads to improved outcomes

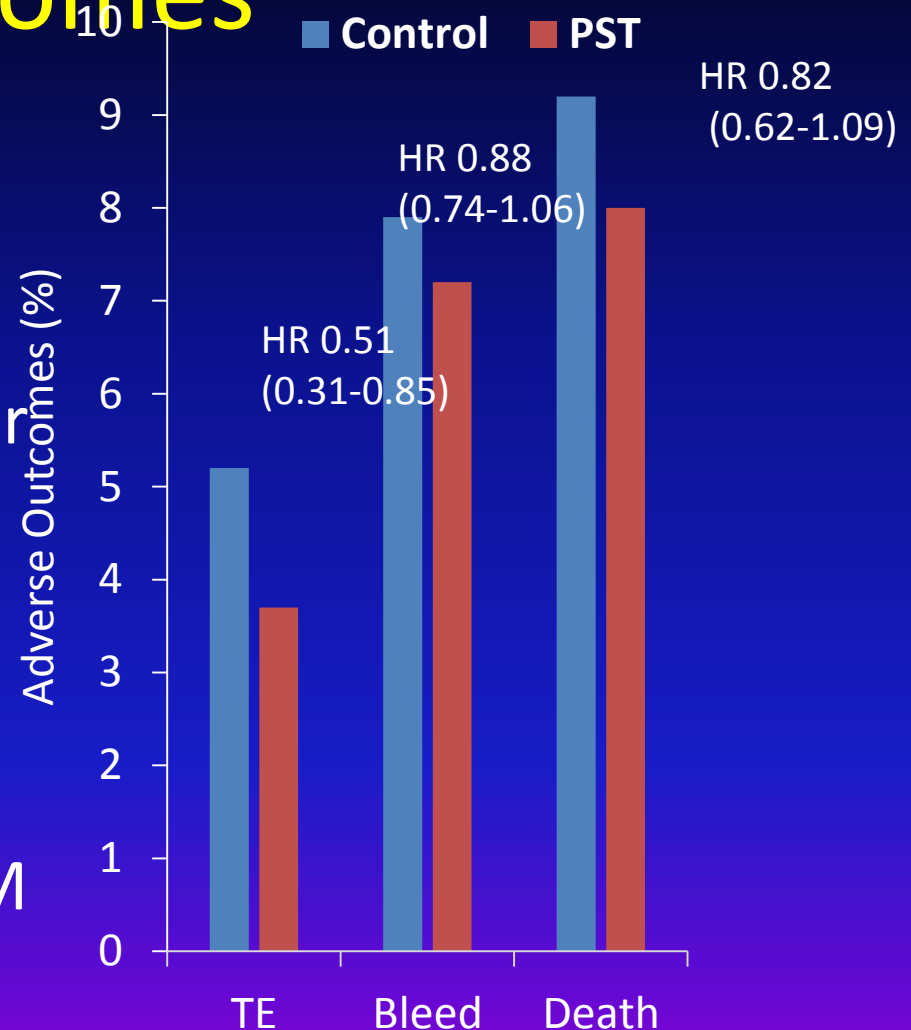
- THINRS- open RCT of AC clinic vs. PST
- Site- 28 VA AC clinics
- Follow up-8730 pt-yrs.
- Test Frequency- PST 7.6 days vs. ACC 23.1 days
- Conclusion- PST associated with greater TTR, patient satisfaction and quality of life

Outcome	PST (N=1465)	Clinic (N=1457)	P Value
Stroke	31 (2%)	31 (2%)	0.83
Major Bleed	147 (10%)	143 (10%)	0.83
Death	152 (10%)	157 (11%)	0.41
TTR	66%	62%	<0.001
DASS	46.8	49.2	0.002
QOL	1.2	1.05	<0.001



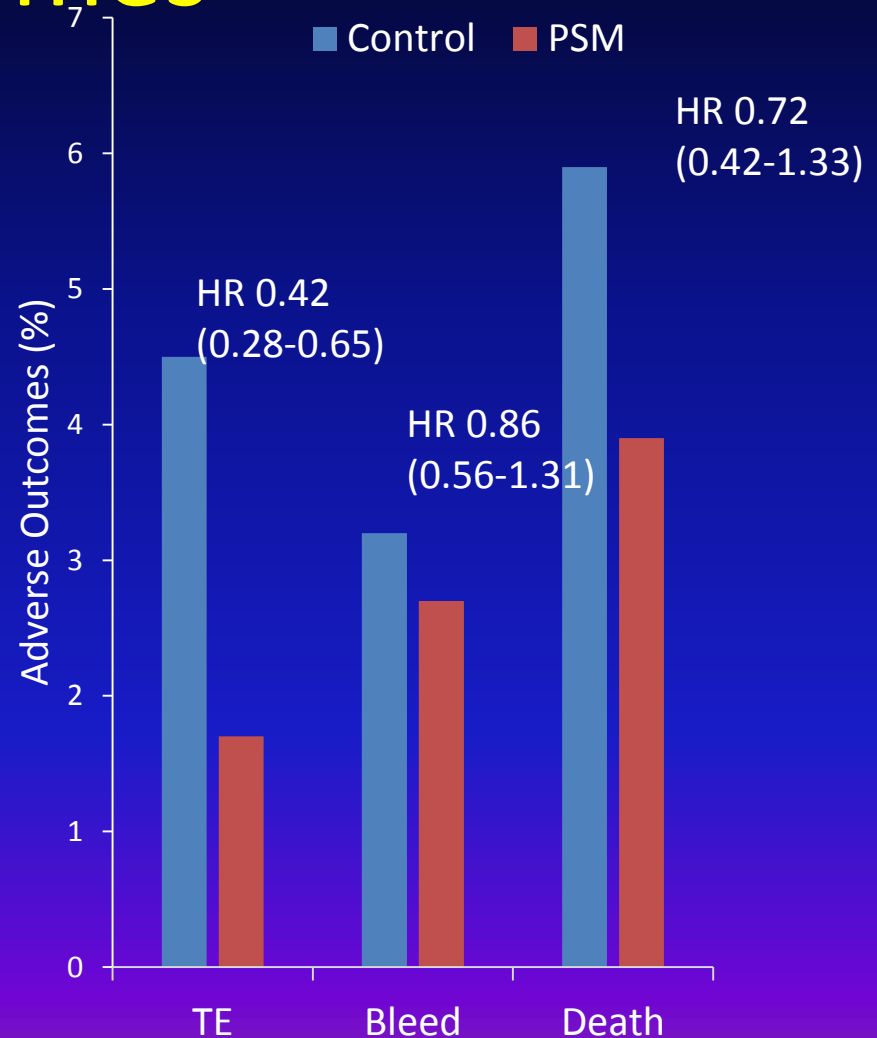
# PST and PSM lead to better outcomes

- Patient level meta-analysis of 11 studies with 6417 pts.
- Thromboembolism lower for pts. < 55 yrs (HR 0.33;0.17-0.66)(NNT 21) and PSM (HR 0.42;0.28-0.65)(NNT 39)
- Conclusion- PST and PSM lead to better outcomes



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# Requirements for a PST/PSM Program

- Provider education (CACP or equivalent)
- Patient education (NPSG compliant)
- POC INR quality assurance program (c/w CAP Guidelines)
- Patient Care Management System
  - Standardized policies/procedures
  - Up-to-date Medical record
  - Patient Care metric tracking
- 24/7 Patient Safety Net

# The Johns Hopkins Anticoagulation Clinic POC INR Program

- Initial visit
  - Medical/surgical history
    - Active medications, allergies, diet, alcohol, cigarette, recreational drug use
  - Vital signs
  - Indication for anticoagulation (site of DVT/PE, triggers, duration of therapy)
  - Patient education on venous thromboembolism, anticoagulation, signs and symptoms of bleeding/thrombosis,
  - POC INR, CBC, aPTT, PT/INR, fibrinogen
    - Lupus inhibitor evaluation if indicated
  - Warfarin dose and return clinic visit

# The Johns Hopkins Anticoagulation Clinic POC INR Program

- Return visits
  - Vital signs
  - Assess/Reinforce patient education
  - Review events since last visit
    - Recent medical illness/invasive procedures
    - Signs or symptoms bleeding/thrombosis
    - Active medication list/medication allergies
    - Medication adherence
    - Diet, alcohol, tobacco, recreational drug use
  - POC INR (+ venipuncture PT/INR and CBC q6 months)
  - Review warfarin dose (with calendar), next clinic visit

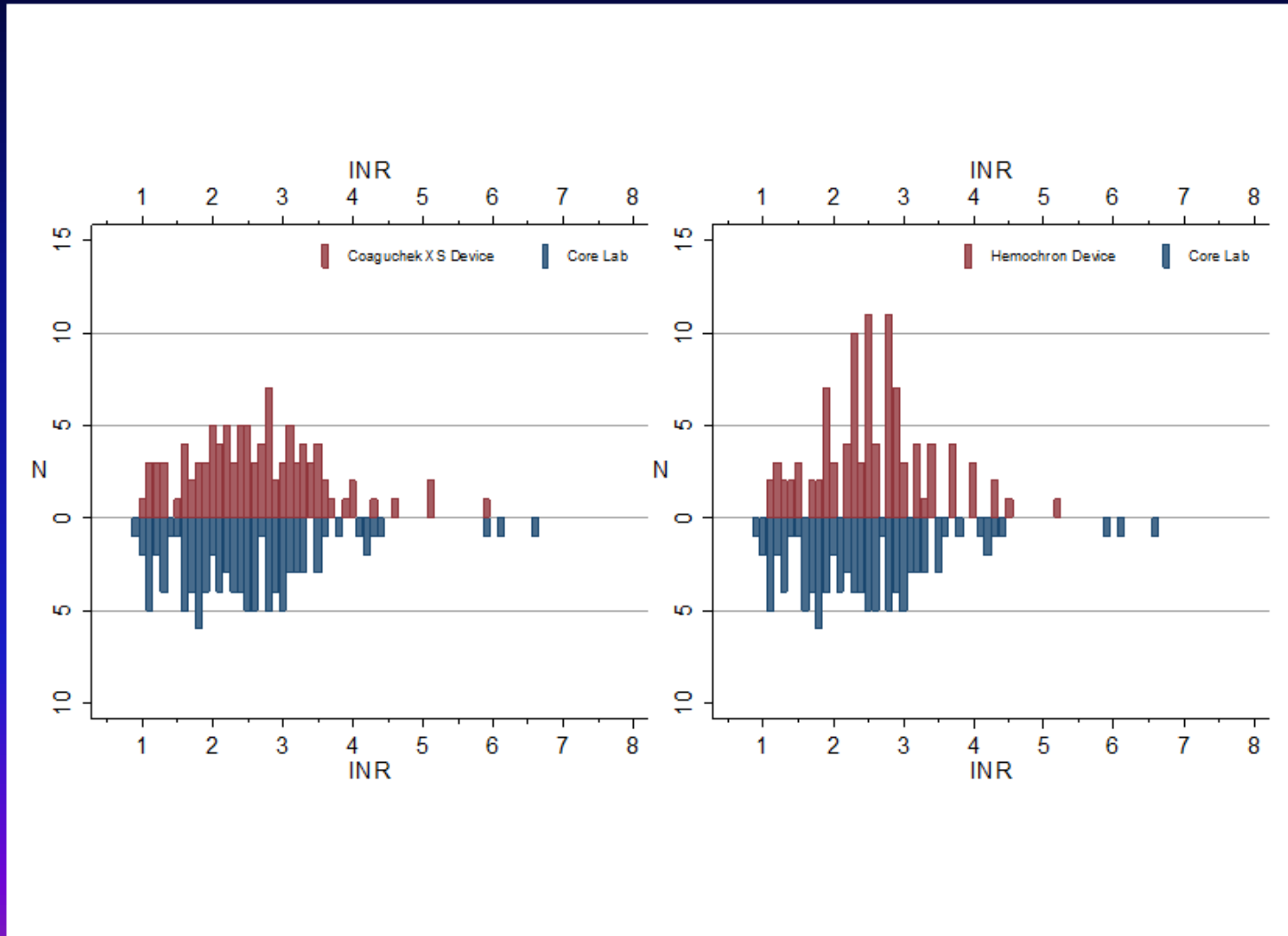
# The Johns Hopkins Anticoagulation Clinic POC INR Program

- Johns Hopkins Clinical Laboratory POC Quality Assurance Program
  - Annual provider testing
  - Daily POC INR monitor controls
  - Ongoing Lab POC Testing QA Monitoring
    - Reagent storage
    - POC INR monitor maintenance
    - Routine comparative venipuncture/POC INR measure assessment
    - Venipuncture INR for all POC INR  $\geq 5$

# The Johns Hopkins Anticoagulation Clinic POC INR Program

- Clinical Anticoagulation Decision-making
  - Weigh risks and benefits of anticoagulation
- Warfarin pharmaco-genomic testing- Not done in our clinic
- Management of critical action value ( $\text{INR} \geq 5$ )
  - Repeat POC INR
  - Obtain venipuncture INR
  - Adjust dose based upon venipuncture INR and etiology of supra-therapeutic INR
- Recalls of POC INR devices
  - Switch to Clinic POC INR until new patient POC INR obtained

# A comparison of two POC INR meters



Shermock K et al. unpublished data



# Impact of Differences on Clinical Decision Making

Method	Below Extended Target INR Range (<1.9)	In Extended Target INR Range (1.9 – 3.3)	Above Extended Target INR Range (>3.3)
Core Lab, n (%)	31 (31%)	55 (55%)	13 (13%)
Coaguchek XS, n(%)	20 (20%)	61 (61%)	18 (18%)
Hemochron, n (%)	16 (16%)	68 (68%)	15 (15%)

30% of decisions based on Hemochron estimated to be different  
18% of decisions based on Coaguchek estimated to be different  
(RR: 1.7, 95% CI: 1.1 – 2.4, p = 0.007)

Shermock K et al. unpublished data

# Who is a good candidate for Patient Self Testing?

- Need for long term anticoagulation
- Adherence to clinic visits and therapy
- Good communication/home support network
- No alcohol or recreational drug issues
- No complicating chronic anemia or coagulopathy
- Completion of POC-INR training program
- Obtain POC INR PST coagulometer (prefer Coaguchek) and enroll in PST program

# Who is a good candidate to continue Patient Self Testing?

- Adherence to home POC INR monitoring
  - Testing on time
  - Good communication with clinic staff
- Adherence to follow up clinic visits (q 3 months)
  - Review POC INR log
  - Review POC INR testing technique
  - Compare POC INR and laboratory INR measures
  - Review routine lab monitoring (e.g., CBC, etc.)

# Barriers to PST Programs

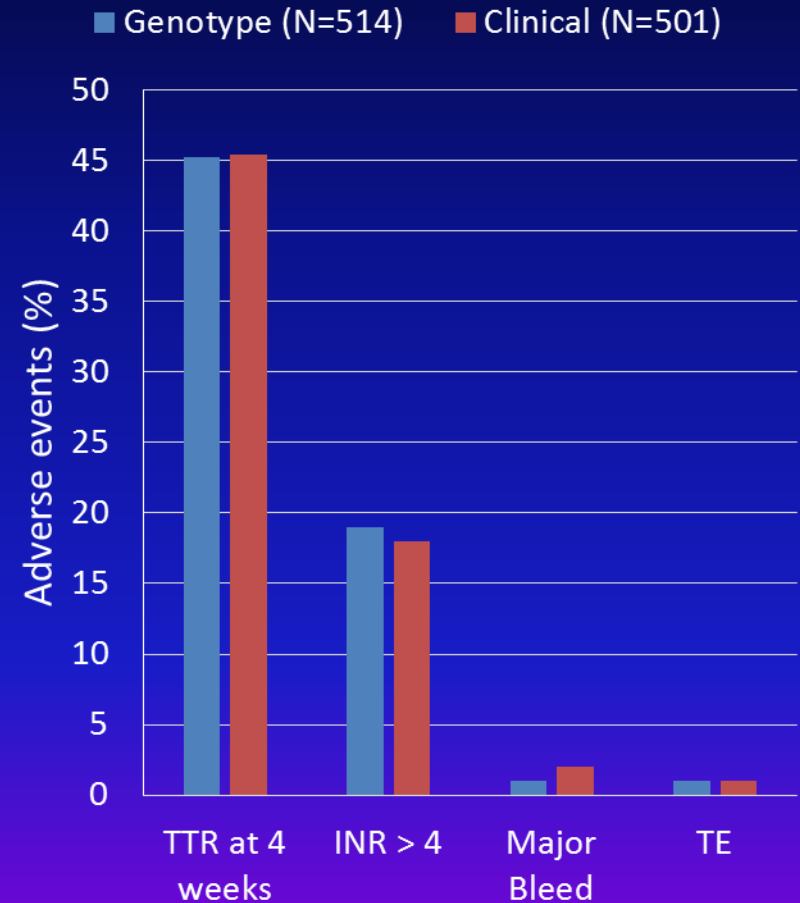
- Patient physical barriers to performing POC INR testing
- Patient competence to perform self-testing
- Patient apprehension about PST or refusal
- Patient insurance coverage to purchase meter and participate in PST program
- Clinic reimbursement for PST

# Should warfarin pharmacogenomic testing be done routinely?

- Warfarin dose requirements influenced by clinical and genetic factors
  - Clinical factors- diet, alcohol, cigarettes, recreational drugs, medications, co-morbid illnesses, adherence
  - Genetic factors- VKORC and CYP 2C9 genotype
- Algorithm incorporating both factors might improve outcomes for patients on warfarin

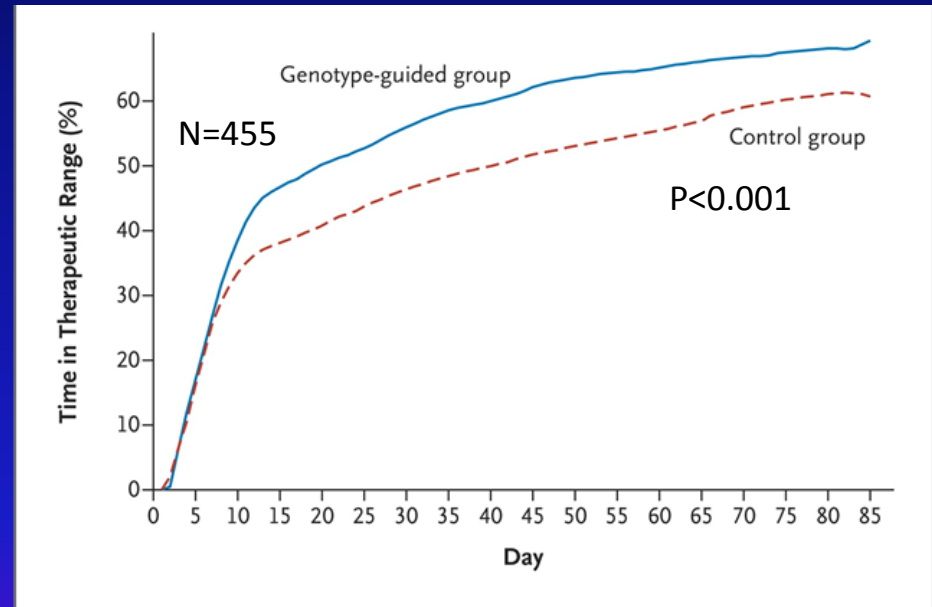
# Should warfarin pharmacogenomic testing be done routinely?

- COAG study- RCT of genotype vs. clinical only dosing algorithm
- Mean age 57
- Male sex 528 (51%)
- African Americans 275 (27%)
- Genotype-guided dosing does not improve outcomes



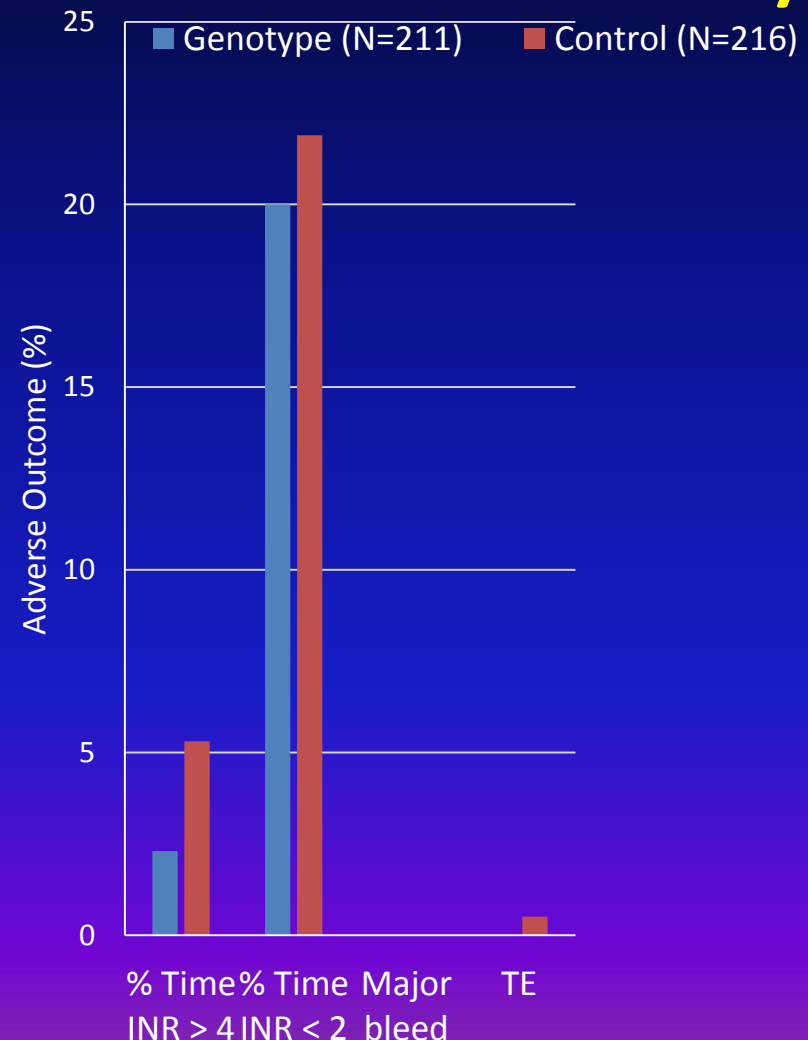
# Should warfarin pharmacogenomic testing be done routinely?

- EU-PACT Trial- RCT of genotype/clinical algorithm vs. fixed dosing
- Outcomes over 3 months
- Mean age 67
- Male sex 277 (61%)
- Black subjects 5 (1.1%)
- Conclusion- Genotype-based dosing associated with higher time in therapeutic range



# Should warfarin pharmacogenomic testing be done routinely?

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# Conclusion

- Warfarin is likely to remain an important anticoagulant for the foreseeable future
- The clinical value of genotype driven warfarin dosing remains uncertain
- Patient self-testing and patient self-management are patient-centered approaches to INR monitoring that are associated with health and quality of life benefits
- Changes in current reimbursement represent a major impediment to PST implementation in the US

Thank you



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**together**

# Point of Care (POC) INR Results and Monitoring of Warfarin Therapy in an Outpatient Based Anticoagulation Clinic

## FDA Public Workshop

Paul T. Kocis, PharmD, RPh, CACP

March 18, 2016

Penn State Hershey Medical Center  
Anticoagulation Clinic

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# Potential Conflicts of Interest

- Alere
  - Project Support
- Pfizer
  - Research Support



# Anticoagulation Clinic (ACC)

- Academic Medical Center
- Pharmacist Managed
- Out Patient Based
- Adult Population
- Direct Patient Care (POC Clinic)
- Tele Management Care



# ACC Responsibilities

- Laboratory INR Management
- Warfarin Dose Management
- Increase/Improve Patient Safety
- Educational Information (written/verbal)
- Reduce Length of Hospital Stay
- Care Coordination
- Transition of Care



# INR Laboratory Source

- Anticoagulation Clinic
- Hospital Laboratory
- Commercial Laboratory
- Physician Office
- Patient Home Testing (POC)
- Visiting Nurses (POC/Venous)





# Benefits of POC Testing

- Home Use
- Convenience / Busy Schedule (e.g., any hour of the day)
- Difficult “Stick” via Phlebotomist
- Routine Frequent Testing (e.g., 1, 2 or 3 times per week)
- Transportation Issues (e.g., no vehicle, or unable to drive due to medical condition)
- Travel with POC Device (e.g., vacation)

# INR Ranges

## Common Diagnoses:

- (2.0 – 3.0) e.g., NVAf, DVT, or PE
- (2.5 – 3.5) e.g., Mechanical Mitral Valve

## Mechanical Circulatory Support:

- (2.0 – 2.5) *or* (2.0 – 3.0) e.g., VAD (Ventricular Assist Device)
- (2.5 – 3.5) e.g., TAH (Total Artificial Heart)

# INR Ranges (cont.)

## Other Diagnoses:

- (2.0 – 2.5) e.g., Orthopedic Patient
- (3.0 – 4.0) e.g., Combination/Multiple Diagnoses

## Medical Complications:

- (2.0 – 2.5) e.g., PMH of Bleeding
- (2.5 – 3.0) e.g., PMH of Thrombosis

# POC INR Result

## Clinical Settings

- ACC (capillary)
- EMER (capillary/venous)

## Decision Making

- *'Exact'* POC INR Result
- *'Approximate'* POC INR Result
- Previous POC INR Experience

# INR Testing Frequency

## Patient Factors

- Frequency
- Compliance
- Adherence
- Money
- Transportation

## “Snapshot” in Time



# Frequency of POC INR Tests

- **Once Weekly**
- **Twice Weekly** (e.g., M/Th or Tu/F)  
*Same Lab Methods/Locations*
- **Twice Weekly**  
(e.g., Monday Lab INR & Thursday POC INR)  
*Different Lab Methods/Locations*
- **Three Times Weekly** (e.g., M/W/F)
- **Once Monthly**

# POC Standard of Practice

- Isopropyl Alcohol Swab vs. Soap/Water
- First/Second Drop of Blood vs. Pipette
- Verify POC INR  
e.g., INR ( $\geq 4$ ) or ( $\geq 5$ )
- LMWH
- Exclude Certain Disease States?

# POC Device Considerations

- Storage of Device (e.g., temperature)
- Storage of Test Strips (e.g., temperature)
- Total Number of Tests Associated with Device
- Report Name of Device Name/Manufacturer with each POC INR test
- Test Interferences (e.g., Medications)
- Medical Condition Interferences (e.g., APS)
- Use of LMWH (e.g., 'bridge')
- Quality Control Internal/External Testing

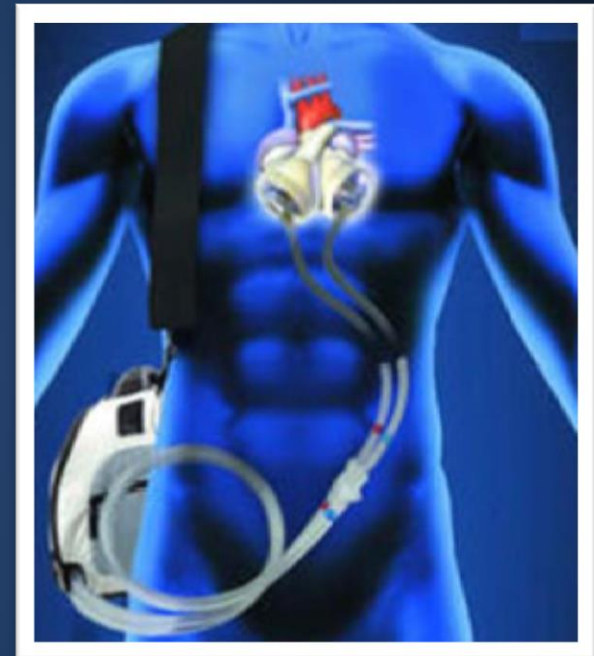
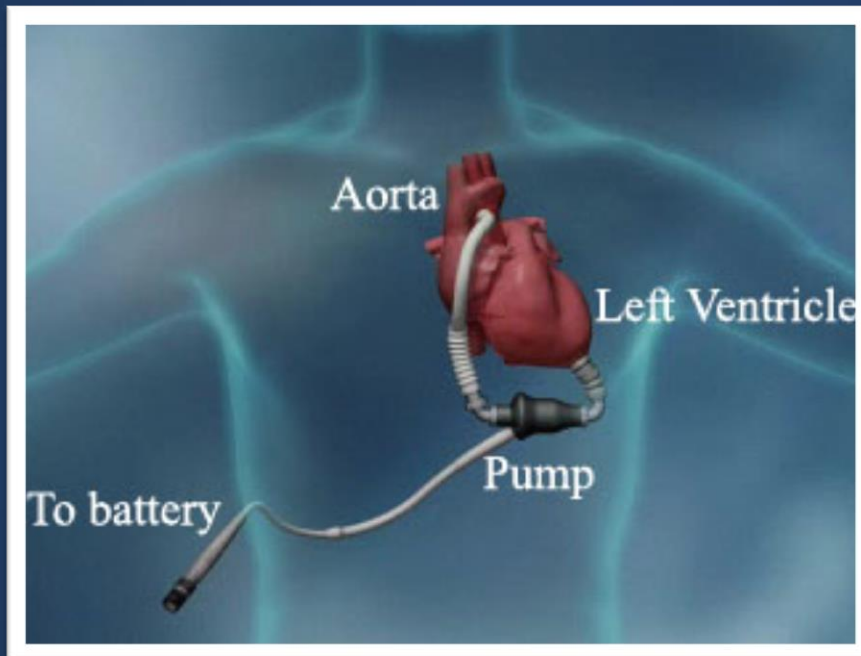


# Patient Populations

- Atrial Fibrillation (NVAf)
- Stroke/TIA
- Deep Vein Thrombosis (DVT)
- Pulmonary Embolism (PE)
- Bioprosthetic/Mechanical Aortic/Mitral Valve
- Ventricular Assist Device (VAD)
- Total Artificial Heart (TAH)

# Mechanical Circulatory Support (MCS)

Ventricular Assist Device (VAD)      Total Artificial Heart (TAH)



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# Unexpected/Unlikely POC INR Result

- Venous specimen INR as the “Gold Standard” reference when comparing to the POC INR result
- Rerun POC test?
- Verify POC INR when ( $\geq 4.0$ ) or ( $\geq 5.0$ )
- International Travel Patient (*warfarin, acenocoumarol, & phenprocoumon*)

# FDA 510 (k) Lab Section

## Studied in 510(k)

- Bilirubin
- Hemolysis
- Triglycerides
- Hematocrit
- Heparin
- LMWH

## Potential for Study

- Fondaparinux
- LDH
- CRP
- Fibrin
- Other Labs?
- Other Medications?

# Penn State Hershey Medical Center Quality Initiative Program

Comparison of the POC  
(Capillary/Venous) INR Result  
with a Corresponding  
Venous INR Result

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# Quality Initiative Program

- Retrospective Review Quality Initiative Program
- Penn State Hershey Medical Center Patients
- Patients  $\geq 18$  years
- Anticoagulation Clinic, Emergency Room, Out Patient, and Unit Based Patients
- Corresponding Capillary/Venous POC INR Specimen & Venous INR Specimen Comparison within 4 Hours on the Same Day

# Quality Surveillance Program

- Anticoagulation Clinic (ACC) POC Test:
  - capillary specimen
- Emergency Room (EMER) POC Test:
  - capillary specimen
  - venous specimen (from syringe)
- Report Generated Weekly on a Sunday for the Preceding (Sunday-Saturday) Timeframe
- Real World Data Collected since 2009



# Quality Management Objectives

Determine if any Statistical Differences in INR testing are related to:

- POC/Venous INR Comparison
- Clinical Setting
- POC Device
- Device Operator



# Quality Program Data Elements

- Clinic (ACC / EMER)
- Gender
- Age
- INR (venous specimen)
- INR (POC) capillary/venous
- Date (of INR)
- Date (of POC INR)
- Time Difference

# Quality Surveillance Program

## Statistical Analysis:

- Real World Use
- (+/-) 5 min & 30 min sub-analysis

## Statistical Analysis Reports:

- Bland-Altman Plot
- Scatter Plot
- Bias
- Percentage Bias

# Summary Data Statistics

Venous INR values within a Specific POC INR Interval:

- N
- Min
- Max
- Mean
- SD

*Example of Report*

	n	min	max	mean	sd
[0.8,1)	7	0.95	1.15	1.046	0.077
[1,1.2)	36	0.94	1.34	1.086	0.087

# Multiple Regression Analysis

## Multiple Regression Variables:

- Clinic Area
- Gender
- Age
- Year Tested
- Time Difference (POC/Venous)

# Laboratory Comparison

- Comparison with Other Lab Analyzers
- Comparison with Other POC Devices
- POC Instrument Software Upgrades



# Time in Therapeutic Range (TTR)

## Calculation of the TTR:

- Rosendaal Method
- Cross Section Method
- Fraction of INR Results Method

# Contact Information

Paul T. Kocis, PharmD, RPh, CACP  
[pkocis@hmc.psu.edu](mailto:pkocis@hmc.psu.edu)

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# FDA Regulation of Point of Care Prothrombin Time/International Normalized Ratio Devices for Monitoring Warfarin Therapy

Randy Fenninger  
CEO, National Blood Clot Alliance  
March 18, 2016



# MY STORY

- Diagnosed with bi-lateral pulmonary embolism in December 2002
- Identified as heterozygous Factor V Leiden
- No previous history or known family history
- Continuous warfarin therapy since 2002
- INR stable within a month of starting therapy
- Always measured on POC PT/INR device
- Alere Home Monitoring of INR initiated in 2009

# Benefits of Home Monitoring

- Device was easy to learn and to use
- Very convenient, no trip to the doctor or the lab
- Designed for dummies
  - Simple operation
  - Simple reporting of results by phone
  - Easy maintenance
  - Easy re-supply of strips, lancets, alcohol swabs
  - Immediate warning if testing was done improperly
  - Written instructions explained error codes, next steps
  - Weekly report on INR improved time in therapeutic range

# Learning to Monitor my INR

- Once home monitoring was approved by my health insurance, training started
- Nurse visited my home and educated me on the device and testing process
- After demonstration of equipment, had to use it to the nurse's satisfaction before it was released
- Nurse followed up later to see if I had questions
- Alere representative called to explain telephone reporting system and supply ordering, written instructions also

# Maintenance of Stable INR

- INR generally stable prior to home testing
- Stability of INR prompted physician decision to move to home testing
- INR remained stable with weekly home testing
- Any INR change could be linked to some other issue, like medication or dietary change
- Because I remained stable on home testing, I concluded that the device worked properly

# Reporting INR Results and Ordering Supplies

- After each test, I called in result to Alere and to my physician
- Automatic voice prompts on Alere system obtained test results, asked how many strips I used and inquired about need for supplies
- Supplies could be re-ordered by phone at the same time
- Simple process and no problems with recording test data or reordering supplies
- Even though the system was automatic, an informed attendant was always available if needed

# Adverse Events

- None while I was using device
- Subsequent recall of strips was communicated to me by phone and letter, even though I was no longer on home testing due to change in my health insurance
- Recall notice continued until I acknowledged receipt of notice by phone

# Possible Device Improvements

- Use of the monitor requires some manual dexterity or assistance by another person
- This limits the number of people who are capable of doing home testing
- Redesign of testing device to facilitate use by people with limited range of motion in hands and arms would be very helpful
- Elimination of finger stick would be nice, but technology would likely be very expensive

# Troubleshooting and Device Quality Control

- Causes of system error or failure
  - Human error
  - Device quality issue
  - Strip quality problem
  - Sometimes hard to determine the cause
  - I experienced all three
  - Is the solution regulation, patient education or some combination?



# Device Quality Control

- Low battery warning
- No obvious way to maintain device calibration or to determine if there was a calibration issue
- If test failed, instructions to repeat with new strip
- Limited written instructions on troubleshooting, but customer service was available by phone
- Only call to customer service resulted in new device being shipped
- Device required brief warm up period before use; was this self re-calibration?
- No comparison with plasma-based laboratory reference test was ever done

# Device Quality Control, cont'd

- Devices designed to be easy for consumer to use, so “troubleshooting” probably best limited to return of defective device and replacement by provider
- Encouraging “Mr. Fixit” to fiddle with device not a good idea
- Increase device’s capability to recognize faults and stop
- Best solution may be clear instructions on when to call to get replacement and prompt response by company
- Obvious test failure was easy to determine through system messages

# Device Quality Control, cont'd

- When device produced a result that was in range, I had confidence in result
- Was that confidence misplaced? How would I know?
- Solution probably is regularly scheduled plasma-based lab reference test
- Convenience is a big factor in favor of home testing so that should not be lost by too many trips to the lab
- Would quarterly be enough? Medical and industry experts could advise

# Contact Information

Randy Fenninger

[rfenninger@stoptheclot.org](mailto:rfenninger@stoptheclot.org)

301-825-9214

# **A Caregiver's Perspective**

**Sue Miller**

**FDA Workshop on Point-of-Care PT/INR Devices  
for Monitoring Warfarin Therapy**

**March 18, 2016**

# About My Dad

- \* My dad, Joe Miller, turned 94 on January 1<sup>st</sup>.
- \* He is a widower, and most of his contemporaries have died. We joke that Dad will outlive us all.
- \* With help from his family (two daughters and four grandchildren), he lives comfortably in his own home.
- \* Despite serious health issues, Dad has an unfailingly positive attitude.

# Current Situation

- \* **Dad's health issues** include a history of heart attack (with little damage to his heart muscle), coronary artery disease, atrial fibrillation, and well-controlled hypertension, hyperlipidemia, and type 2 diabetes.
- \* **Dad's medications** include Warfarin, Metoprolol, Metformin, Glipizide, Atorvastatin, low-dose aspirin and a multivitamin. He has been on the same drug regimen for several years.
- \* **Dad started taking Coumadin/Warfarin in 2005**, when he suffered a mild heart attack. His doctors found major blockage in Dad's carotid artery, but considered surgery too risky at his age. They chose to manage Dad's condition with Coumadin instead.

# Device Information

- \* **We started home-testing in early 2012.** My dad's cardiologist prescribed weekly tests and made all the arrangements for us. At the time, his office preferred Philips for INR testing. As long as we are compliant, Dad's insurance (Medicare) covers equipment and supplies.
- \* Our first machine was manufactured by Alere and was an **INRatio device**. Initially, we reported to Philips, until they sold the division to Remote Cardiac Services. Until this month, when we changed providers, we reported to RCS.
- \* Starting in January, we switched to a different reporting service (Alere Home Monitoring). They provided us with a next-generation testing device, **CoaguChek XS**, manufactured by Roche.
- \* We now test two-to-four times per month and submit our results to Alere, which in turn provides our results to Dad's INR nurse. When Dad is out of range, she calls me to make recommendations.



# INR Stability (1)

- \* Since my dad has a history of serious falls, his cardiologist wants his INR between 2.0 and 2.5. His nurse will accept a few ticks above or below that mark occasionally.
- \* Even with a narrow target range, Dad is often in range. When he is out of range, his numbers tend to be lower rather than higher.
- \* Dad generally has a healthy appetite. At first, we restricted his diet, but he complained vigorously. His current diet is consistent from week to week, but not limited in any way.
- \* In the summer, Dad usually eats more fruits and vegetables, and his INR fluctuates as a result. For some reason, Dad's INR was unusually variable this past summer. Dad's INR nurse thought it might be the machine.

# INR Stability (2)

- \* Our first reporting service could be diligent in an unpleasant way. If I didn't report Dad's INR within seven days, I would get a “dunning” call the morning of the eighth day. While I appreciate reminder calls, I resented the accusatory tone of these calls.
- \* When I complained to Dad's INR nurse, she said I wasn't alone. She said she'd switched many of her patients to another reporting service, but since we did reasonably well on our existing service, she would keep us on it.
- \* Two things happened that changed her mind: 1) the real possibility that our first-generation device was inaccurate; and 2) her own problems communicating with the company. In mid-2015, she switched us to a new reporting service, which we started using in January.

# Quality Control (1)

- \* About a year ago, patients using the INRatio device were notified that some users were getting inaccurate INR results. The reporting service said it was a “software problem” and suggested patients get bloodwork to ensure they weren’t affected. Dad’s INR nurse read or heard about the problem weeks before the company notified her. She was concerned about her patients and called us immediately. She was appalled the reporting service had not notified providers promptly.

# Quality Control (2)

- \* Occasionally, I took Dad's INR immediately after a doctor's visit to check that the results were similar. The few times I compared results, they were the same, but I had no way of knowing week after week if Dad's readings on the older machine were accurate.
- \* With our new CoaguChek device, I insert a coded chip with each new batch of strips to verify the accuracy of every reading. Although it adds a step to the test, this feature looks promising.

# Benefits

- \* **Convenience:** Without home-testing, it would be hard to take a 94-year-old who is unsteady on his feet for weekly or even monthly INR checks. I don't drive, which would make clinic visits even more difficult.
- \* **Diet:** With weekly readings, Dad's INR nurse is able to tweak Dad's dose to return him quickly to range. As a result, he is able to eat a normal (and healthy) diet.
- \* **Doctor-patient relationship:** I appreciate Dad's nurse's attention to his case and her regular calls when Dad is out of range. In my opinion, home-testing strengthens Dad's relationship with his doctor and leads to better care.

# Challenges

- \* Sometimes I have difficulty getting a reading, which is nerve-wracking. I'm unsure what various error messages mean. If error codes were universal, I could google them for a solution.
- \* I usually take Dad's INR after business hours. While I can call a staff person the next day, I sometimes want quicker answers to questions. For example, if I have trouble getting a valid reading, do I keep trying until I get a number? If I quit after three tries, will I get a nasty call the next morning?

# Additional Questions (1)

***Does the current device labeling adequately and clearly describe the proper use, risks and benefits of the device in a language you can understand?***

- \* Yes, but I confess I don't read every document that comes with a new device. I usually follow the "quick start" guide and skim user's manuals.
- \* When we got our first device, a Philips technician came to my dad's home to show my sister and me how to use the machine and get an accurate INR reading. We were given written materials, which we reviewed and then filed and forgot.
- \* I've just started using the CoaguChek device. It comes with extensive educational materials, plus a secure website filled with useful information. My dad's nurse did not order training for us since I'm a seasoned home-tester.
- \* We learned about stroke and bleeding risks and the importance of a stable INR from Dad's cardiology nurse. I don't recall reading about risk in the labeling.

# Additional Questions (2)

***How do you acquire more testing strips? Is this a difficult process? And what do you do with the test results?***

- \* With our previous service, I called to order strips or lancets when we needed them. We were eligible for one batch of six strips every six weeks. A company representative said they'd had problems at the factory and were no longer able to send nine strips with every order. We paid out of pocket for a reserve supply, and the company reluctantly filled the order.
- \* To report Dad's INR, I called an automated 800 number with Dad's test results. I entered Dad's patient ID, his PIN, and his two-digit result.



# Additional Questions (3)

***How do you acquire more testing strips? Is this a difficult process? And what do you do with the test results? (continued)***

- \* We started using a new reporting service in January. I am able to order supplies online or by phone. According to the “patient responsibility agreement,” reorder is based on the test results we report.
- \* To report Dad’s INR, I go to a secure website and provide Dad’s patient ID, PIN and date of birth to sign into his account. Then I enter Dad’s INR, the date I tested it, and how many tries it took. The website stores Dad’s test results, so we are able to review his history.

# Additional Questions (4)

***Does anyone contact you about your test results?***

***What preventative actions do you take?***

- \* My dad's INR nurse calls when Dad is out of range. She generally asks about Dad's diet for the week and whether he missed any pills before she adjusts his dose.
- \* Dad's standard Warfarin dose is 2 mg five days per week and 2.5 mg twice per week. If Dad's INR is low, she'll ask Dad to replace one or more 2 mg pills with 2.5 mg pills. If his number is high, she'll reduce his dose slightly. We usually go back to Dad's standard dosage if he's in range (or very near it) the next week.
- \* I'm sure some patients object to third-party reporting, but it works well for us.

# Additional Questions (5)

***What communication barriers have been encountered and how do you recommend these barriers be mitigated?***

- \* Not every phone call from our first reporting service was unpleasant. Occasionally, they called to “check in.” Mostly, they pushed regular testing, but these conversations were still useful. Perhaps phone calls once or twice a year to update users on new devices and options and to answer technical and other questions would help.

# Additional Questions (6)

## ***What could advance the development and use of POC PT/INR medical device patient labeling?***

- \* I generally look online when I have a question about my other devices. Depending on the issue, I look for a searchable user's manual or for a list of Frequently Asked Questions (FAQs). I often find answers to my questions, especially if the material is clearly presented. Oddly, I've never looked online for INR device questions, but I haven't been directed there either.

# Conclusion

- \* For patients on Warfarin, home-testing makes a real difference. It minimizes everything wrong with the drug and makes it much easier to take.
- \* In my experience, the drawback with home-testing is its rigidity. I'm conscientious about taking my dad's INR, but I'm not (and never will be) perfect. If my dad's cardiologist allows a more flexible schedule, it seems the testing service should as well.

# Session 1: Clinician and Patient Perspectives

**Q&A**

**Docket No. FDA-2015-N-4462**



# BREAK

**Docket No. FDA-2015-N-4462**



## Session 2

### Quality Assessment

**Moderator**

**Niquiche Sangster-Guity, PhD**

*Scientific Reviewer*

*Hematology Branch*

*Division of Immunology and Hematology Devices*

*OIR/CDRH/FDA*



# POC and Lab INRs

Why do they differ?

Marcia L. Zucker, Ph.D.  
ZIVD LLC

# INR

## ● International Normalized Ratio (INR)

- > ISI = international Sensitivity Index
- > INR target ranges are specified by indication
  - Individual variation based on patient history

$$INR = \left( \frac{PT_{patient}}{PT_{meannormal}} \right)^{ISI}$$

# Key variables

## ● ISI

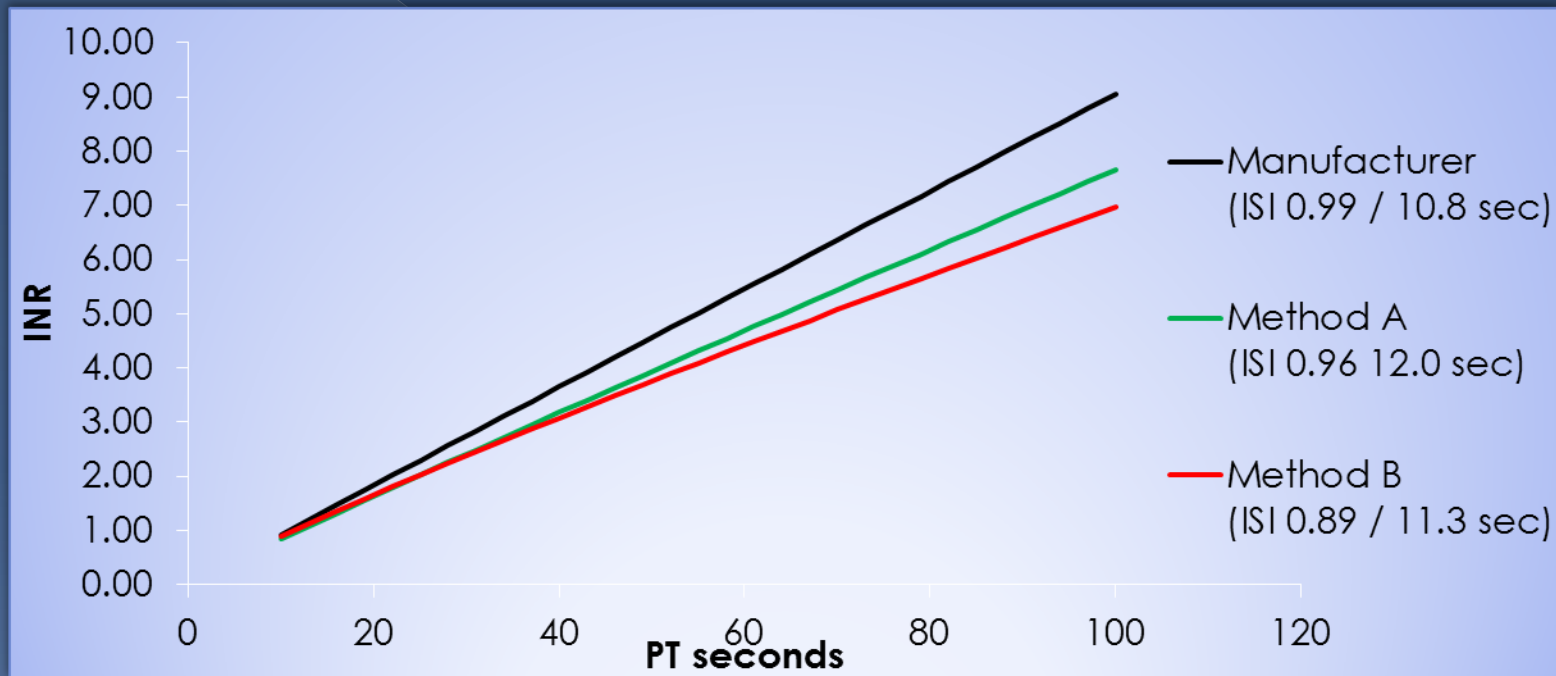
- Initially determined by reagent manufacturer
- Traceable to IRP
  - International Reference thromboplastin Preparation
- WHO defined process
  - Calibration up to INR = 4.5
  - manual tilt tube method reference
- Local calibrations can be performed to determine the instrument specific ISI<sup>1</sup>

## ● Mean normal PT

- The mean normal PT should be determined for each new batch of thromboplastin with the same instrument used to assay the PT<sup>1</sup>

# Effect of Local Calibration

- Local calibration may introduce variability

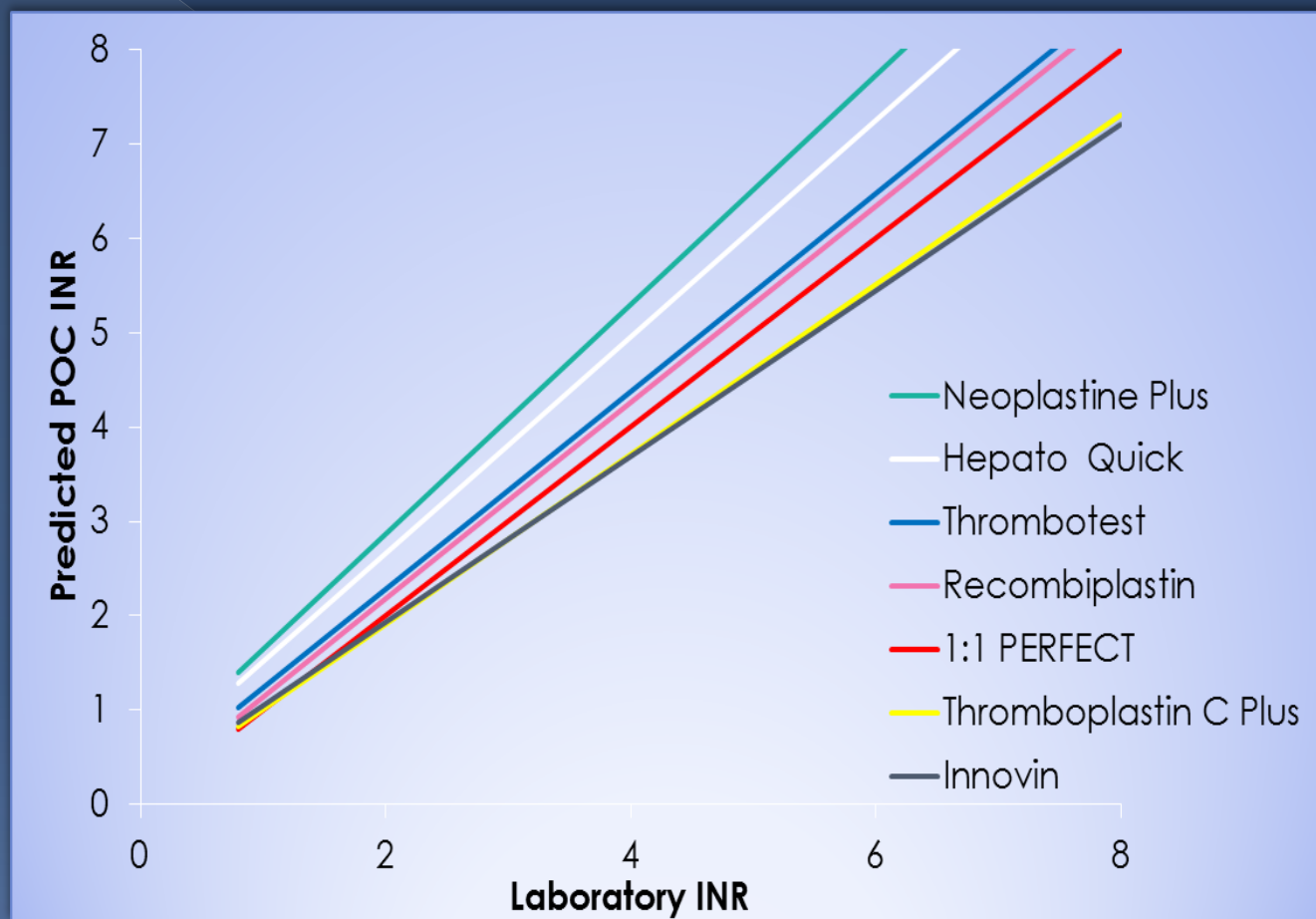


- > Same sample yields different results depending on calibration method

# POC Calibration

- Manufacturer assigns ISI and mean normal PT (MNPT)
  - > Lot specific
- Traceable to IRP
  - > Often through secondary standard
- Cannot be changed by end user
  - > Does not vary by location of testing

# Correlation by lab system



Correlation data from:  
Plesch et. al, Thromb Res  
2008; 123:381-9

Thromboplastin	Analyzer	calibration	Thromboplastin	Analyzer	calibration
Innovin	CA1500	Local vs rTF/95	HepatoQuick	STA-R	Manufacturer
Recombiplastin	MLA1800	Local vs rTF/95	Thrombotest	KC10	Local vs OBT/79
Neoplastin Plus	STA-R	Manufacturer	Thromboplastin C Plus	CA1500	Manufacturer

# Variables affecting lab and POC

## ● Endpoint

- > Physical clot
- > Surrogate endpoint

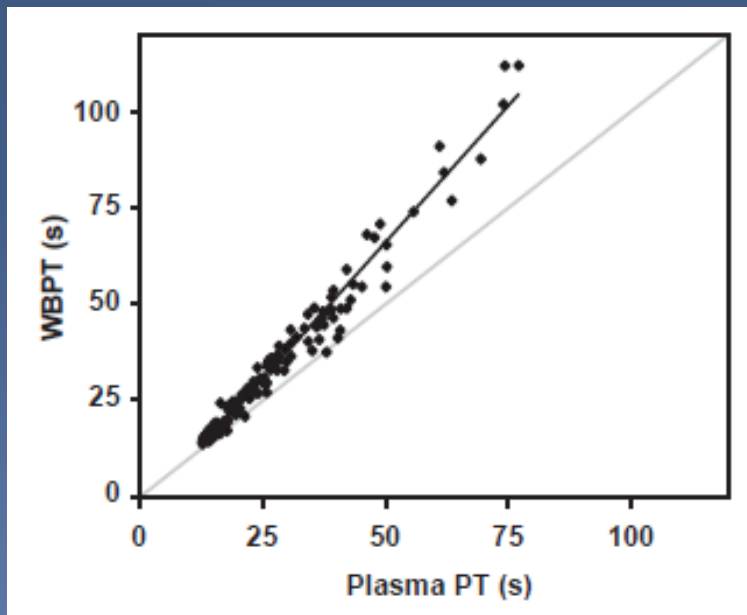
## ● Detection

- optical
  - turbidity or flow
- mechanical
- electrochemical
- pressure

# POC vs Lab: differences

## ● Sample

- Whole blood versus platelet poor plasma
  - *in vivo* much of the coagulation cascade occurs on the platelet surface



Using the same sample volume, WBPT values were on average 40% longer than plasma PT values  
>50% for INR

Increased sample volume and adjusted ISI led to equivalent results

$$\text{WBINR} = 0.99(\text{plasma INR}) - 0.02$$
$$r^2 = 0.98$$



# POC vs Lab: differences cont'd

## ● Hematocrit

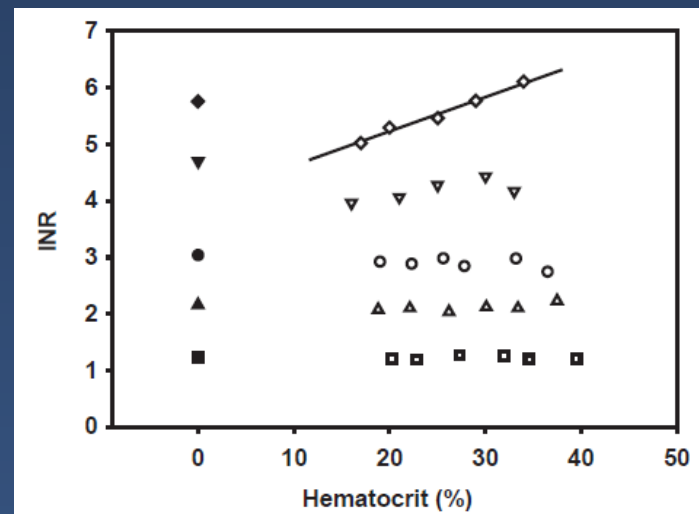
- Largest impact at high INR

## ● Dilution

- > No anticoagulant vs sodium citrate
- > Dry reagent vs addition of liquid reagent
- > Lab addition of calcium to initiate coagulation

## ● Preanalytical delay

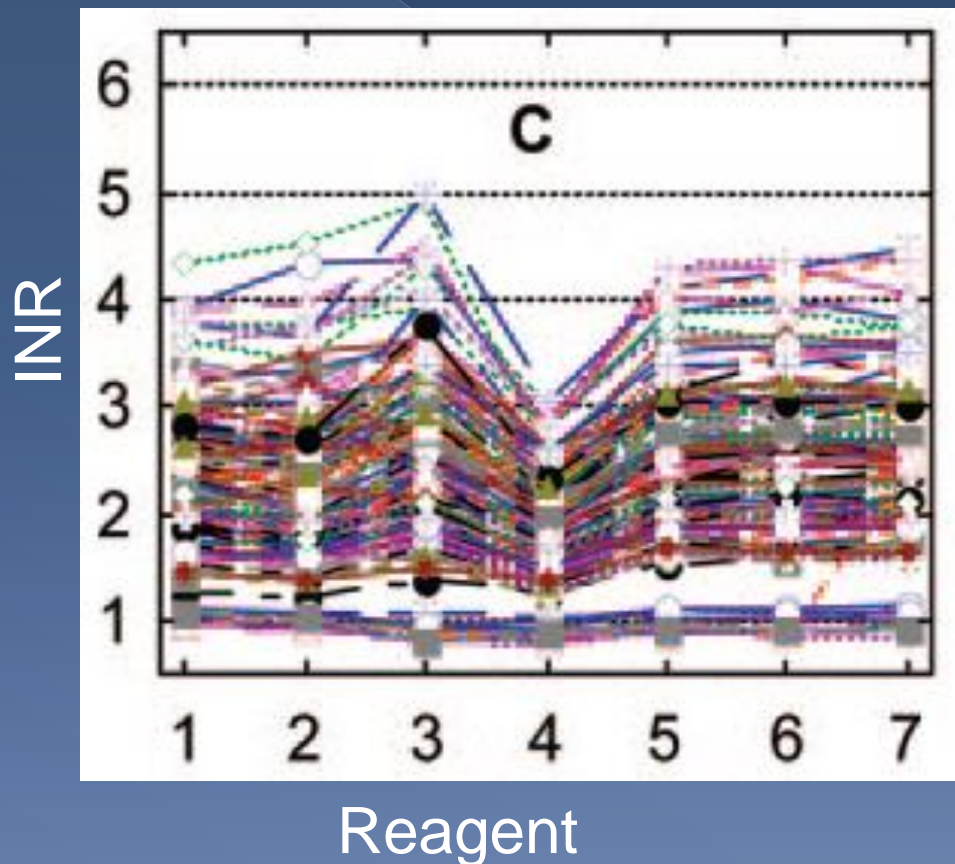
- Sample transport and storage
  - May differ by reagent/ instrument<sup>2</sup>



<sup>2</sup>CLSI H21-A5 Collection, transport and processing of blood specimens for plasma based coagulation assays and molecular hemostasis assays

# Expectations Lab to Lab

- 150 samples measured with 7 lab reagents
  - 1 calibration method for all reagents

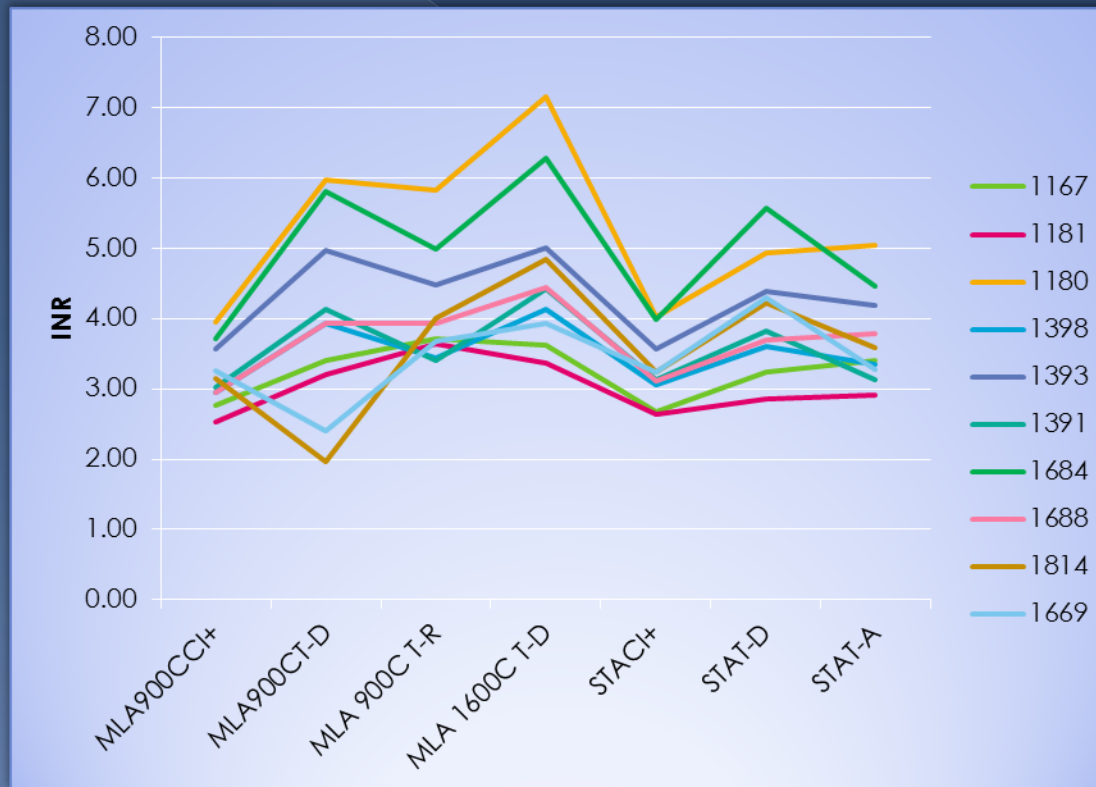


Horsti, et. al. 2005; *Clinical Chemistry* 51:553–560 (2005)

# Expectations Lab to Lab - 2

- 10 OAT patients across 7 analyzer/reagent combinations

- McGlasson, DL 2003: Lab Med 34: 124 – 9.



# Expectations Lab to Lab - 3

## ● 95 OAT patients

- McGlasson, DL 2003: Lab Med 34: 124 – 9.

Instrument	Reagent	Mean INR Vendor ISI	Mean INR Local ISI
STA	Neoplastine Cl+	2.58	2.69
	Thromborel S	2.56	2.58
	Thromboplastin C+	2.39	2.15
	Innovin	2.45	2.67
CA 540	Neoplastine Cl+	3.46	2.90
	Thromborel S	2.69	2.58
	Thromboplastin C+	2.82	2.60
	Innovin	2.49	2.25
BCS	Neoplastine Cl+	2.81	2.60
	Thromborel S	2.67	2.57
	Thromboplastin C+	2.86	2.51
	Innovin	2.66	3.29

# Expectations

- Similar results whether lab to lab or POC to lab compared

- Jacobson, AK. 2008: J Thromb Thrombolysis 25:10–11

Mean INR	Range
2.0	$\pm 0.4$ INR
3.0	$\pm 0.8$ INR
4.0	$\pm 1.2$ INR

# Expectations POC to lab

## ● Evaluation of 4 POC devices

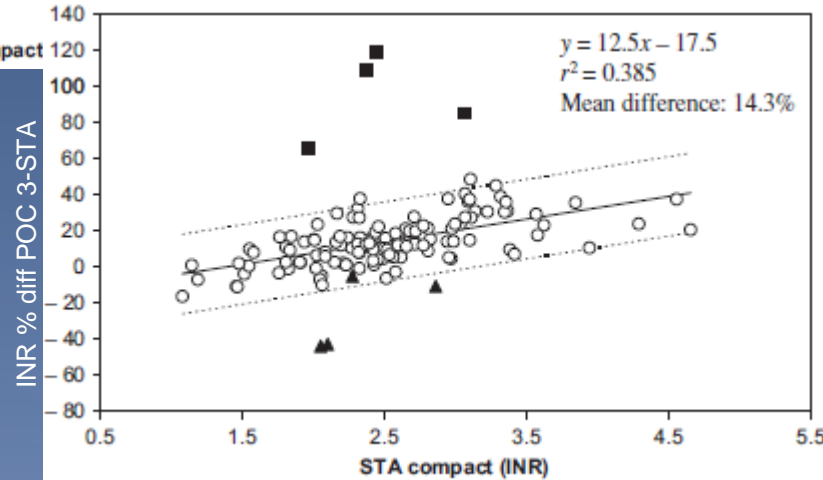
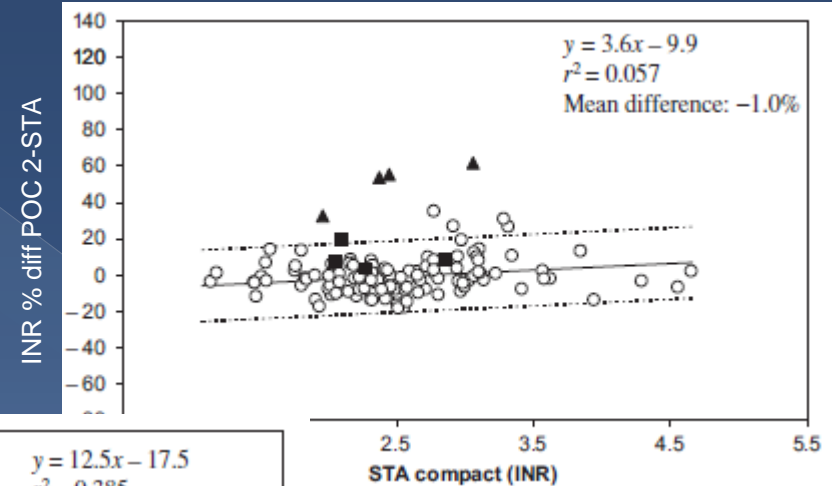
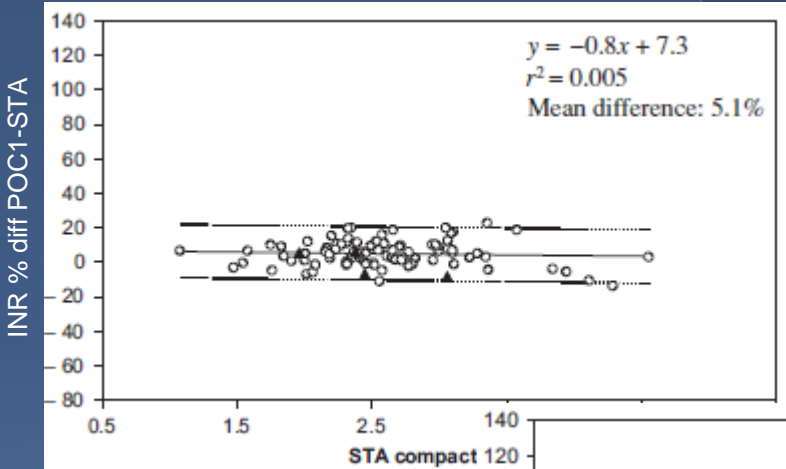
> tilt tube; all INR <4.5

- van den Besselaar et al. 2015 Thrombosis Research 135:526–531

	INR <2.5 (N=32)		INR >2.5 (N=28)	
	Mean INR	Bias (%)	Mean INR	Bias (%)
rTF/09	2.14		2.87	
POC 1	2.12	-0.9	2.84	-1.0
POC 2	2.32	8.4	3.20	11.5
POC 3	1.92	-10.4	2.40	-16.2
POC 4	1.94	-9.3	2.61	-9.0

# Expectations POC to lab

- 36 patients over 4 visits each
  - 3 POC; 1 lab
    - Solvik et. al., 2010: Clin Chem 56:1618–1626 (2010)



# Summary

- Use of the INR improves prothrombin time standardization
  - > INR does not completely standardize the measurement
- INR variability increases with increasing INR
  - > Lab to Lab or
  - > POC to Lab



# Conclusions

- Performance requirements must be defined which recognize the inherent variability of the INR system.

# Thank you

Marcia L. Zucker, Ph.D.  
ZIVD, LLC  
mlzucker@verizon.net



COLLEGE of AMERICAN  
PATHOLOGISTS

# Point of Care PT/INR

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## Technical Limitations and Laboratory Accreditation Issues

Russell Higgins, MD, FCAP  
Associate Clinical Professor,  
University of Texas Health Science Center San Antonio  
Interim Medical Director of University Health System Pathology Services

# Disclosure

**Russell Higgins, MD, FCAP**

**Chair, CAP Coagulation Resource Committee**

**Travel, Food, and Lodging reimbursed by the CAP**

# Objectives

- **Recognize limitations of the INR (International Normalized Ratio) system**
- **Compare point of care (POC) and central lab methods**
- **Identify interferences of POC PT/INR (PT=prothrombin time)**
- **Review proficiency testing performance**
- **Review relevant laboratory accreditation issues**

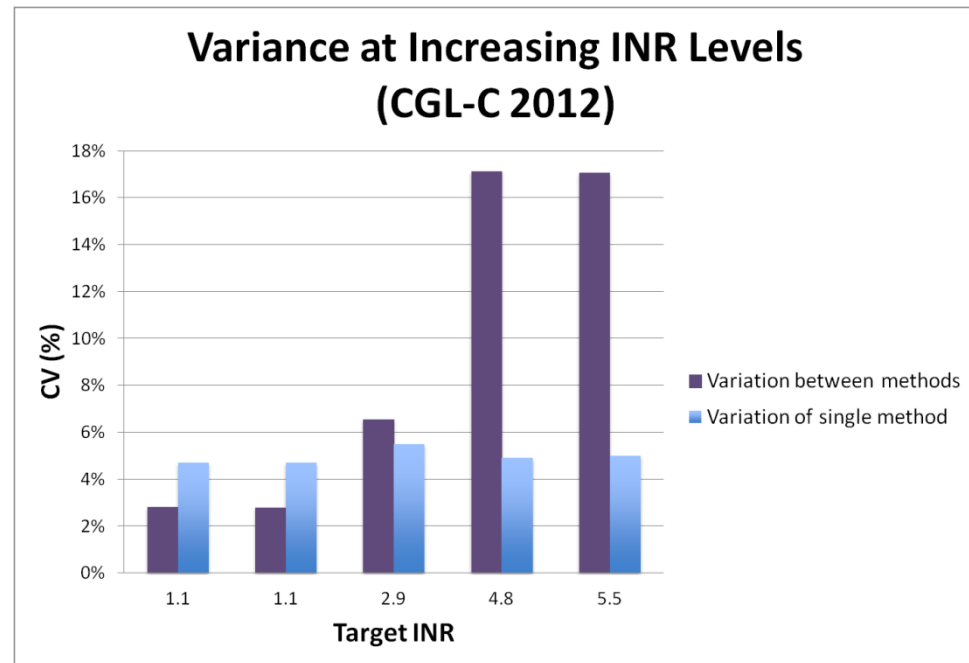
# INR Does Not Harmonize INR above 4.5

- CAP Survey CGL-B 2015
- High level abnormal INR sent to all participants
- Wide variability in INR

International Normalized Ratio				
REAGENT/INSTRUMENT	NO. LABS	MEAN	S.D.	C.V.
DIAG STAGO NEO CI PLUS				
DIAG STAGO ST4,STRT4/8	29	8.09	1.04	12.8
DIAG STAGO STA COMPACT	1105	6.88	0.42	6.1
DIAG STAGO STA SATELLITE	149	7.00	0.38	5.4
DIAG STAGO STA-R/EVOLUTN	304	6.71	0.38	5.7
HEMOSIL PT-FIB HS PLUS				
IL ACL 7000 & UNDER	61	5.72	0.37	6.4
IL ACL 8/9/10K, ELITE/PRO	18	5.96	0.39	6.5
IL ACL TOP SERIES	8	-	-	-
HEMOSIL PT-FIB				
IL ACL 7000 & UNDER	34	6.35	0.80	12.6
IL ACL 8/9/10K, ELITE/PRO	43	6.35	0.50	7.9
IL ACL FUTURA/ADVANCE	9	-	-	-
HEMOSIL RECOMBIPLSTN 2G				
DIAG STAGO STA COMPACT	20	4.97	0.37	7.5
IL ACL 7000 & UNDER	8	-	-	-
IL ACL 8/9/10K, ELITE/PRO	283	5.38	0.32	6.0
IL ACL FUTURA/ADVANCE	23	5.33	0.32	6.0
IL ACL TOP SERIES	880	5.29	0.31	5.8
SEKISUI				
SEKISUI COAPRESTA 2000	8	-	-	-
SIEMENS INNOVIN				
DIAG STAGO STA COMPACT	19	4.24	0.25	5.8
DIAG STAGO STA SATELLITE	12	4.33	0.25	5.8
SIEMENS BCS, BCS XP	223	4.37	0.26	5.9
SIEMENS/SYSMEX CA-SERIES	1477	4.19	0.26	6.1
SIEMENS/SYSMEX CS-SERIES	27	4.31	0.27	6.3

# INR Does Not Harmonize INR above 4.5

- No cross-platform certified plasmas
- Limits of certified plasmas 1.5 to 4.5
  - Most laboratories report INR up to ~8.0
  - Reportable range would not be covered



Current INR system doesn't harmonize values >4.5 between methods

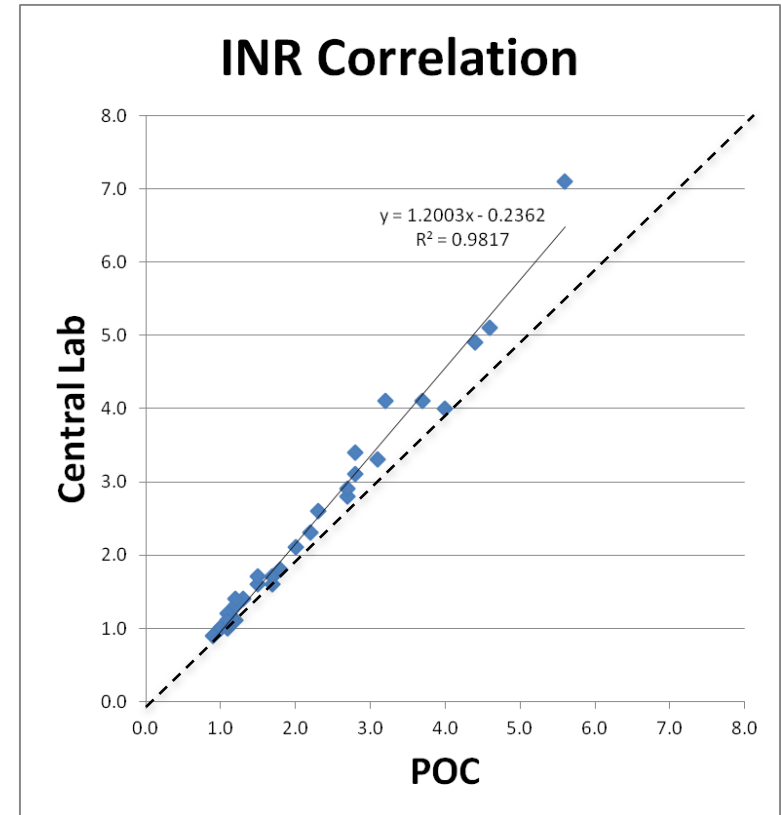
# Overreliance on INR above 4.5

- **Kcentra® approved for warfarin reversal**
  - **Dose schedule based on INR of 2 - <4 ; 4 - 6, and >6**
- **\*Chest Guidelines**
  - **For patients taking warfarin therapy with INR 4.5 - 10 and with no evidence of bleeding, we suggest against the routine use of vitamin K**
  - **INR >10 and with no evidence of bleeding, we suggest oral vitamin K...**



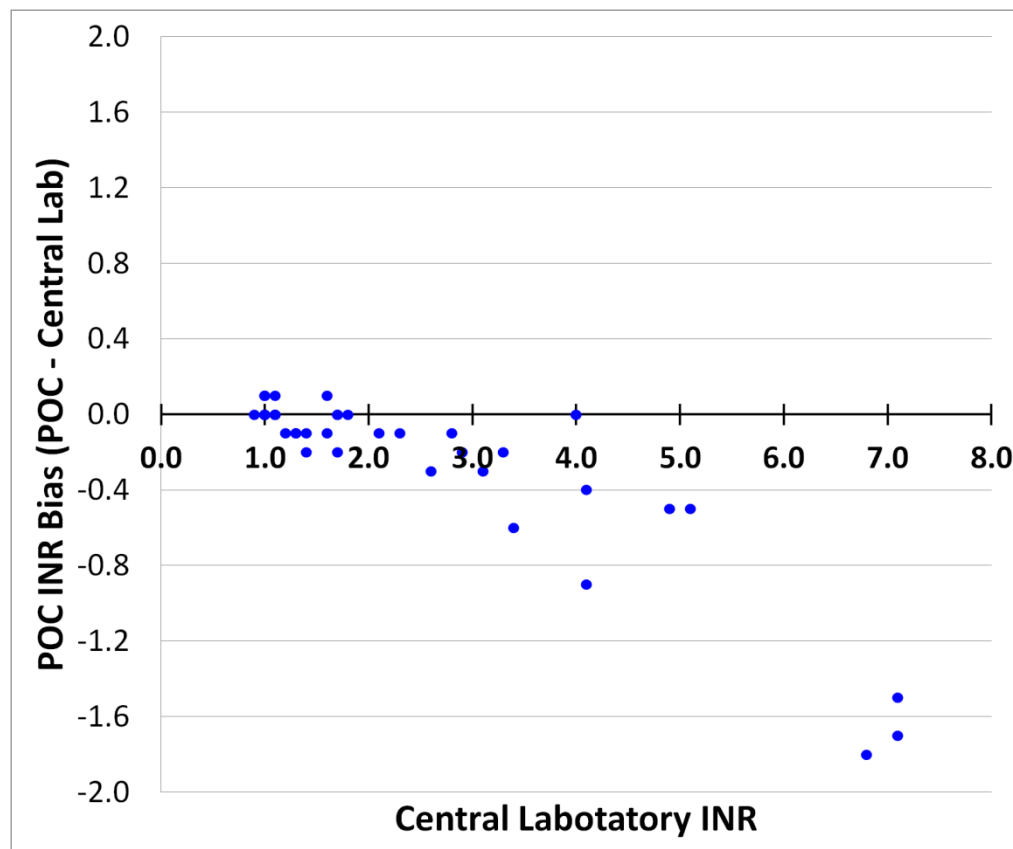
# POC INR: Method Comparison

- POC Vs. Central Lab
  - Almost always linear
    - High  $R^2$
  - Line of identity (or slope) demonstrates bias



# POC INR: Method Comparison

- **POC vs. Central Lab**
  - **Bias Plot for INR**
    - Good correlation for lower INR values
    - Poor correlation for high INR values

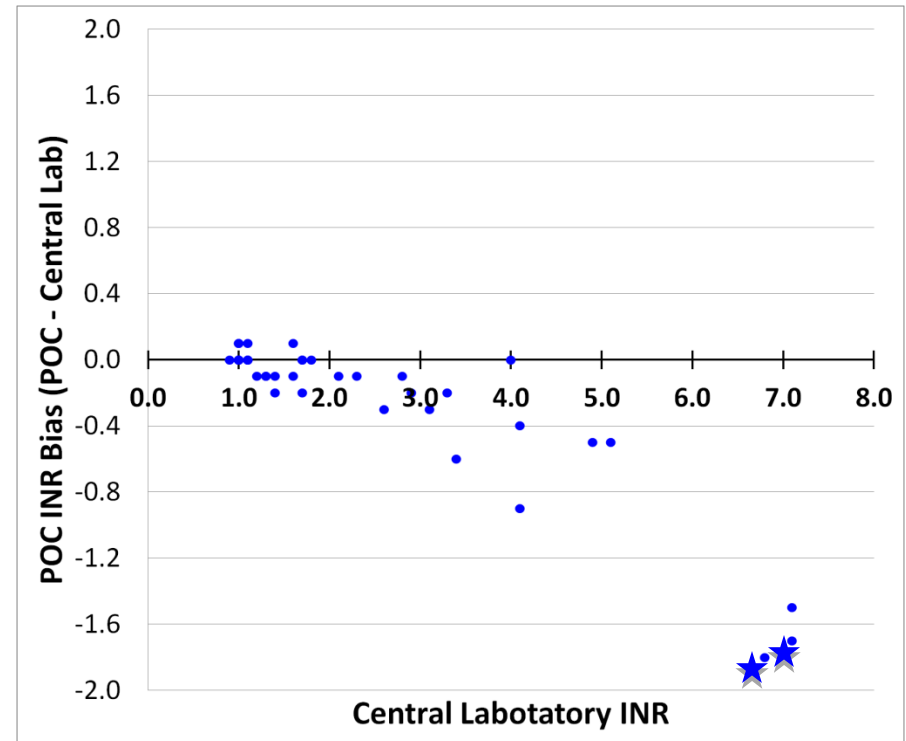


# POC INR: Complaint from the Warfarin Clinic

- ...”significant result (POC INR) differences compared to blood draws (central lab INR)”

- Examples

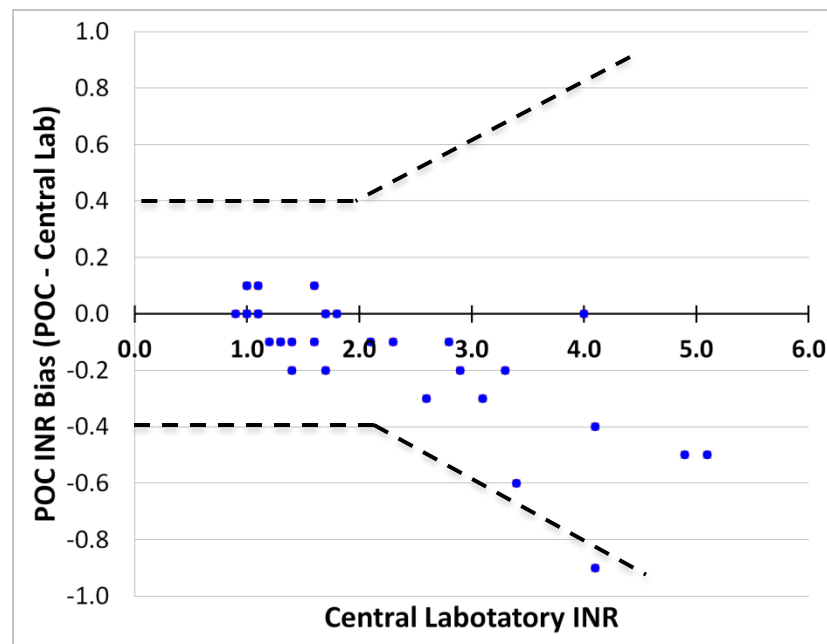
- 5.4 (POCT) versus 7.1 (Lab)
- 5.0 (POCT) versus 6.8 (Lab)



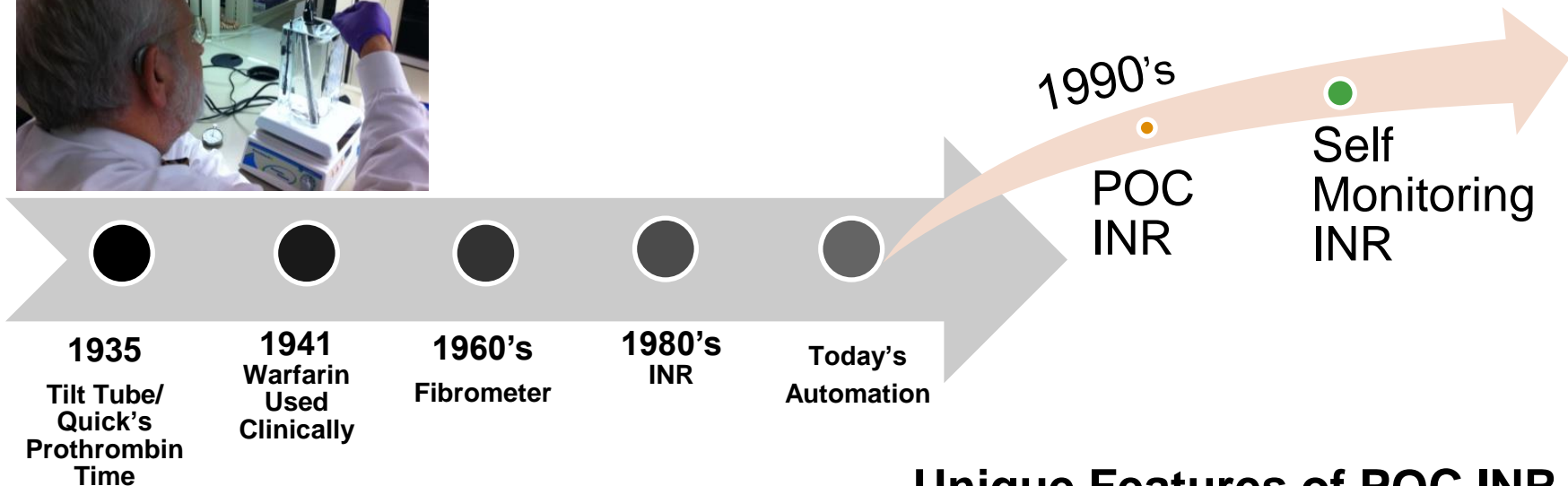
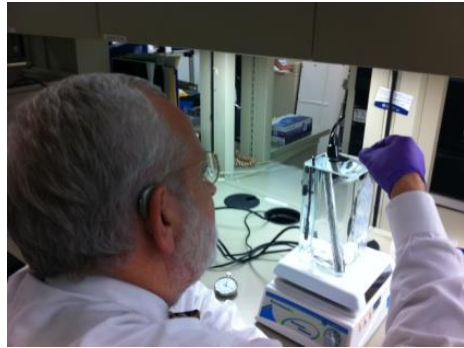
# POC INR: Assessing INR Agreement

- Laboratory
  - Absolute Difference
    - e.g.  $\pm 0.4$
  - % Error
    - e.g.  $\pm 20\%$  error
- Self-Testing
  - ISO 17593:2007
    - $\pm 0.5$  for INR  $< 2$  and...
    - $\pm 30\%$  for INR 2.0 - 4.5
    - Very Broad; more stringent criteria have been proposed

\*Determined by  
Medical Director



# Evolution of POC INR



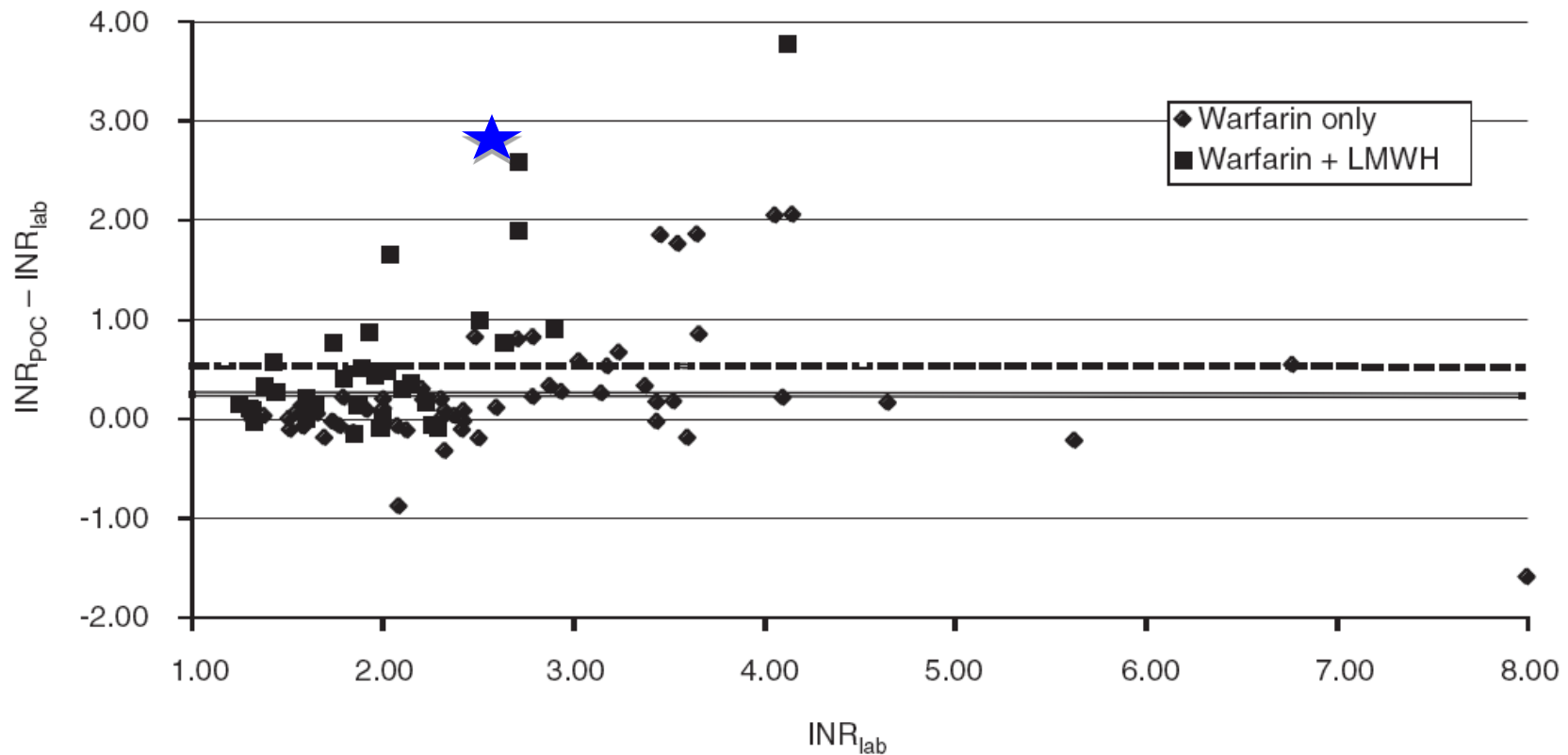
## Unique Features of POC INR

- Fingertick or venous whole blood
- Different end point detection
- Different reagents (eg. Lack heparin neutralization)
- ISI is programmed on chip or test card

# POC INR: Case Presentation

- 45 year-old male with venous thromboembolism (VTE) treated with low molecular weight heparin (LMWH) and now bridging to warfarin
- POC INR = 5.2
  - \*Sample sent to central lab to verify “unusual result”
  - Central Laboratory INR = 2.7

# POC INR: Interferences/LMWH



# INR: Interferences/Heparin

- **Central Laboratory INR**
  - Heparin neutralized up to ~0.8 IU/ml
  - LMWH may not be neutralized as effectively
  - Used for bridging warfarin and heparin therapy
- **POC INR**
  - Variable claims about heparin interference
  - Limited literature on effect of heparin + warfarin
  - POC INR indicated for monitoring warfarin rather than initiating warfarin therapy



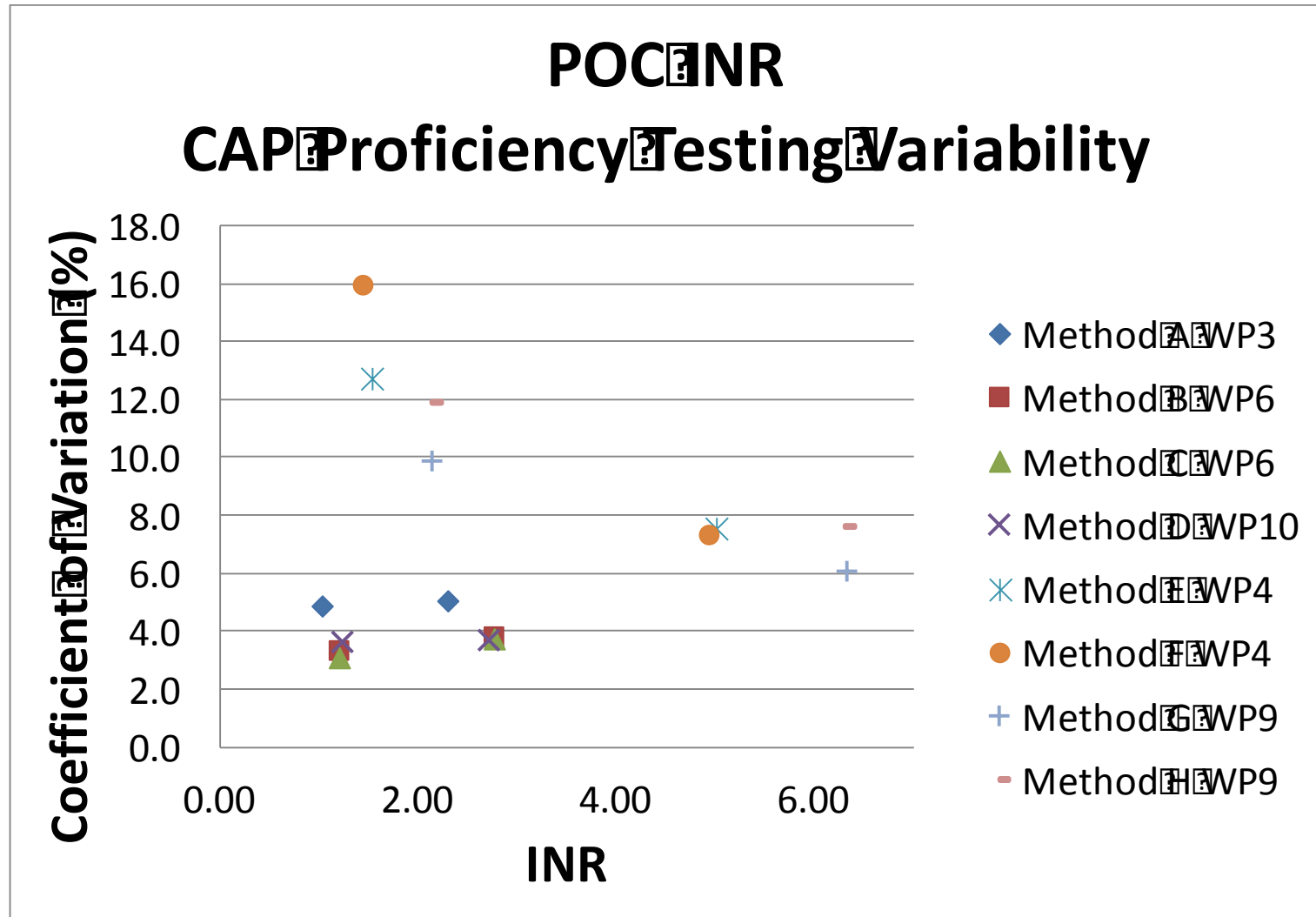
# INR: Common Interferences

- **Lupus anticoagulant**
- **Parenteral anticoagulants**
  - **Hirudin, bivalirudin, argatroban, UF heparin, LMWH**
- **“New” oral anticoagulants**
  - **Dabigatran, rivaroxaban, apixaban**
- **Bilirubin**
- **Hemolysis**
- **Lipemia**
- **Low or elevated hematocrit**

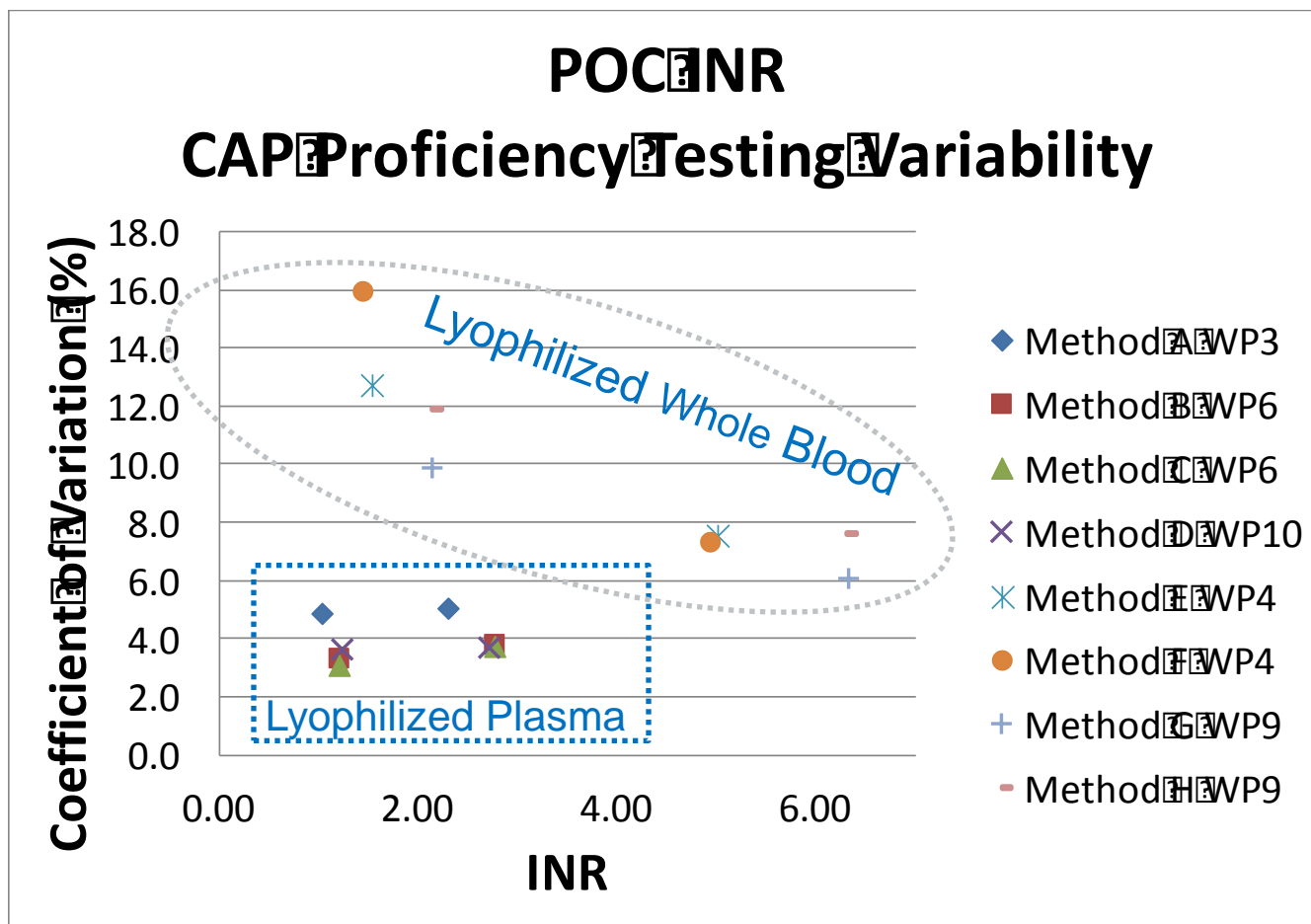
# CAP Proficiency Testing: POC PT/INR

- 5 separate surveys (WP3, WP4, WP6, WP9, WP10)
  - Supports different volume requirements
  - Supports different sample types
    - Lyophilized plasma
    - Lyophilized whole blood, noncitrated
    - Lyophilized whole blood, citrated
  - Multiple surveys and sample types make it difficult to compare device performance

# Proficiency Testing: Intra-Method Variability



# Proficiency Testing: Intra-Method Variability



# Frequently Cited CAP Checklist Deficiencies: Quality Control – Nonwaived Testing

- **POC.07300 Daily QC - Nonwaived Tests**      **Phase II**
  - Controls are run at least daily...
  - % Cited Using Checklist -- 86/1839 (4.7%)
- **POC.07550 Monthly QC Review**      **Phase II**
  - Quality control data are reviewed and assessed at least monthly...
  - % Cited Using Checklist -- 78/1703 (4.6%)
- **POC.07512 QC Handling**      **Phase II**
  - Control...are tested...by the same personnel as patient samples.
  - % Cited Using Checklist -- 61/1839 (3.3%)
- **POC.07211**      **Phase II**
  - ...controls are reviewed for acceptability before reporting results
  - % Cited Using Checklist -- 3/136 (2.2%)

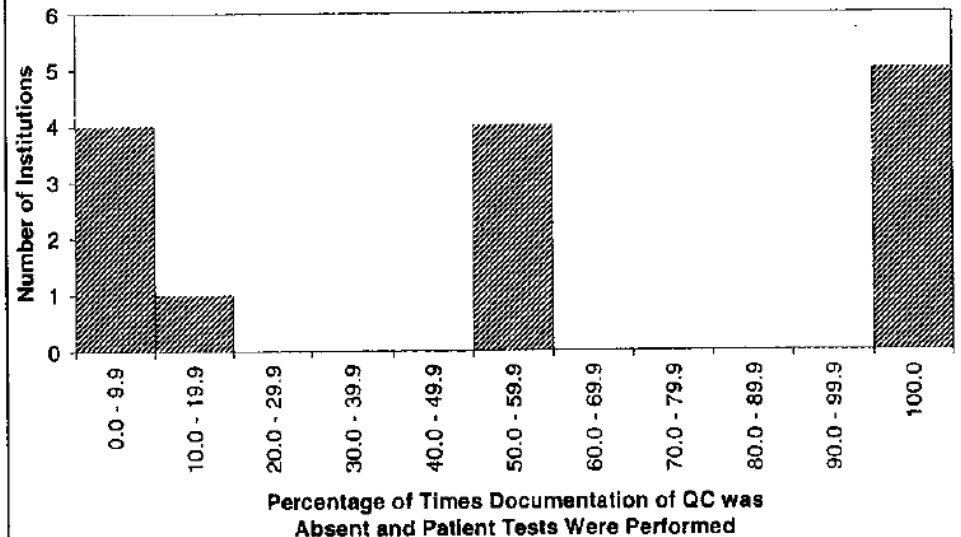
# Frequently Cited CAP Checklist Deficiencies: Quality Control -- Waived Testing

- **POC.07037 Documented QC Results - Waived Tests Phase II**
  - The laboratory follows manufacturer instructions for quality control, reviews results, and records acceptability prior to reporting patient results.
  - % Cited Using Checklist -- 84/1839 (4.6%)

# CAP Q-Probe: Point-of-Care Coagulation Testing (99-04)

- Of 80 participants 66 performed all expected quality control (QC)
- The 14 remaining labs reported instances of patient testing when QC was not documented

Figure 5.— Distribution of all participants' percentage of times documentation of QC was absent and patient tests were performed (N=14 institutions\*).



\* Of the 80 participants that submitted the necessary data to calculate this measure, 66 reported no occasions where required QC was not performed during the study period.

# CAP Q-Probe: Point-of-Care Coagulation Testing (99-04)

- Laboratory personnel were more likely to perform expected QC compared to nursing personnel
  - Decentralized testing
  - Less focus on quality control and corrective action

**Table 5.— Association between personnel that most often performs and documents QC and rate of expected QC events that were performed.**

Personnel Type	Number of Institutions	All Institutions Percentiles				
		10th	25th	50th (median)	75th	90th
Nursing personnel	48	75.0	96.3	100.0	100.0	100.0
Laboratory personnel	18	100.0	100.0	100.0	100.0	100.0
Other	17	97.3	100.0	100.0	100.0	100.0



# POC INR: Relevant CAP LAP Requirements

- **POC.06875Competency Assessment - Waived**
- **POC.06910Competency Assessment – Nonwaived**
  - % Cited Using Checklist -- 143/1839 (7.8%)

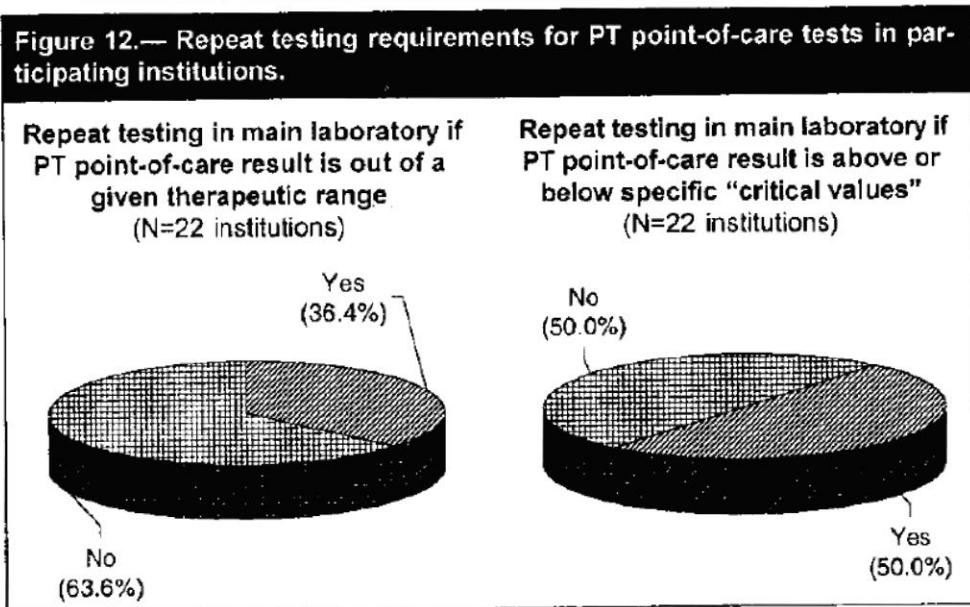


# POC INR: Relevant CAP LAP Requirements

- **POC.03800**

## Troubleshooting Responsibilities

- Backup testing
  - e.g. Refer INR > 4.5 to central laboratory
- Trained individuals available for troubleshooting



**CAP Q-Probe: Point-of-Care Coagulation Testing (99-04)**

# POC INR: Relevant CAP LAP Requirements

- **POC.03810 Manufacturer Instructions**

- **Indications**

- Most POC PT/INR tests are indicated for monitoring warfarin only
    - Use for identifying factor deficiency (eg. PT for perioperative coagulopathy) is a modification of manufacturer instructions

# POC INR: Relevant CAP LAP Requirements

- **POC.03700 Unusual Laboratory Results**
  - Correlated unexpected test results with clinical findings
    - e.g. Therapeutic INR and unusual low dose of warfarin
  - Procedure should address analytic interferences
    - Bridging from heparin or LMWH
    - Non-warfarin anticoagulants can't be monitored by INR
    - Monitoring warfarin for Antiphospholipid Antibody Syndrome
    - Excluding other interferences

Thank you!

# **CLIA and POC PT/INR Devices**

**Sarah F. Bennett, MT (ASCP)**  
**CMS/CCSQ/SCG**  
**Div. of Laboratory Services**  
**March 18, 2016**

# Objectives

At the end of the presentation, you should be able to understand:

- The general process of a CLIA survey
- Specific survey activities related to POC PT/INR devices
- CLIA competency assessment
- Issues related to POC PT/INR devices

# General CLIA Survey Process

- CLIA surveyors use the outcome-oriented survey process
- Scheduling of surveys
- Entrance and tour of the laboratory
- Evaluation of lab operations and activities
- Exit conference
- Mandatory citations
  - Personnel Qualifications
  - Proficiency Testing



# General CLIA Survey Process

- Personnel qualifications
- Pre-analytic
- Proficiency testing enrollment and performance
- Verification of performance specifications
- Quality Control (QC)
- Quality Assessment (QA)
- Competency assessment (CA)
- Post-analytic

# General CLIA Survey Process

- Laboratories issued a CLIA certificate must permit a survey to assess the laboratory's compliance with CLIA requirements.
- CMS may require the laboratory to do the following during a survey:
  - Test samples or perform procedures
  - Permit interviews of all personnel
  - Permit laboratory personnel to be observed performing all phases of testing
  - Permit access to all areas included in the CLIA certificate
- All records and data must be accessible and retrievable
- A laboratory must provide all information and data needed to determine compliance

# Survey Activities: POC PT/INR

Examples of what surveyors may look at:

- Manufacturer package insert
- QC Documentation
- Corrective Action, QA
- Testing Personnel Competency
- Verification of Performance Specifications
- Strip/Cartridge lot numbers
- Storage of cartridges, reagents
- Placement of device

# Competency Assessment (CA)

**Competency** is the ability of laboratory personnel to apply their skill, knowledge and experience to perform their duties correctly.

**Competency assessment** is used to ensure that laboratory personnel are fulfilling their duties, as required by Federal regulations.

**Competency assessment** is a regulatory requirement.

# CA Rationale

- Confirms training effectiveness
- Helps ensure test performance is consistent
- Part of overall quality management
- Helps to prevent errors

# CA: Six Required Procedures

1. Direct observation of testing
2. Monitoring test results
3. Review of records
4. Direct observation of preventive maintenance and function checks
5. Previously analyzed specimens
6. Problem solving skills

# POC PT/INR: Pre-analytic Issues, Fingertick Examples

- Cold hand/poor circulation
- Milking the finger
- Contaminated finger
- Bruised, swollen finger
- Not drying site
- Improper lancet depth
- Re-sticking the same site
- Double dropping
- Smearing blood on strip
- Micro capillary tube
  - bubbles or scraping

# POC PT/INR: Pre-analytic Issues, Venipuncture Examples

- Vein above an IV site
- Using vein near a hematoma
- Using fistula/shunt
- Tourniquet on too long
- Not following order of draw
- Using incorrect blue top tube (3.8% citrate instead of 3.2%)
- Shaking the tube
- Underfilling/overfilling the tube
- Not following timing and storage requirements



# POC PT/INR: Analytic Issues

- Devices and reagents not stored per manufacturer requirements
- Incorrect lancets being used
- Specimens drawn with a butterfly → transferred to red top tube with no anticoagulant → pipetted onto device

# POC PT/INR: Post-analytic Issues

- Unacceptable QC recorded as acceptable
- Error messages recorded as QC
- QC not documented
- Inaccurate relationship between PT and INR
- Incorrect result entered into patient record

# Summary Slide

- Surveyors look for compliance with CLIA requirements
- Preanalytic issues with PT/INR testing can be significant
- Good training and competency assessment programs help ensure high quality results
- Most noncompliance issues are related to following the manufacturer instructions and performing quality control

# Session 2: Quality Assessment

## Q&A

**Docket No. FDA-2015-N-4462**



# LUNCH

**Docket No. FDA-2015-N-4462**



# Session 3

## CDRH Perspective

**Moderator**

**Cheng Zhang, PhD, MBA**

*Branch Chief*

*Hematology Branch*

*Division of Immunology and Hematology Devices*

*OIR/CDRH/FDA*

# FDA Regulatory Oversight of POC PT/INR *In Vitro* Diagnostic Devices

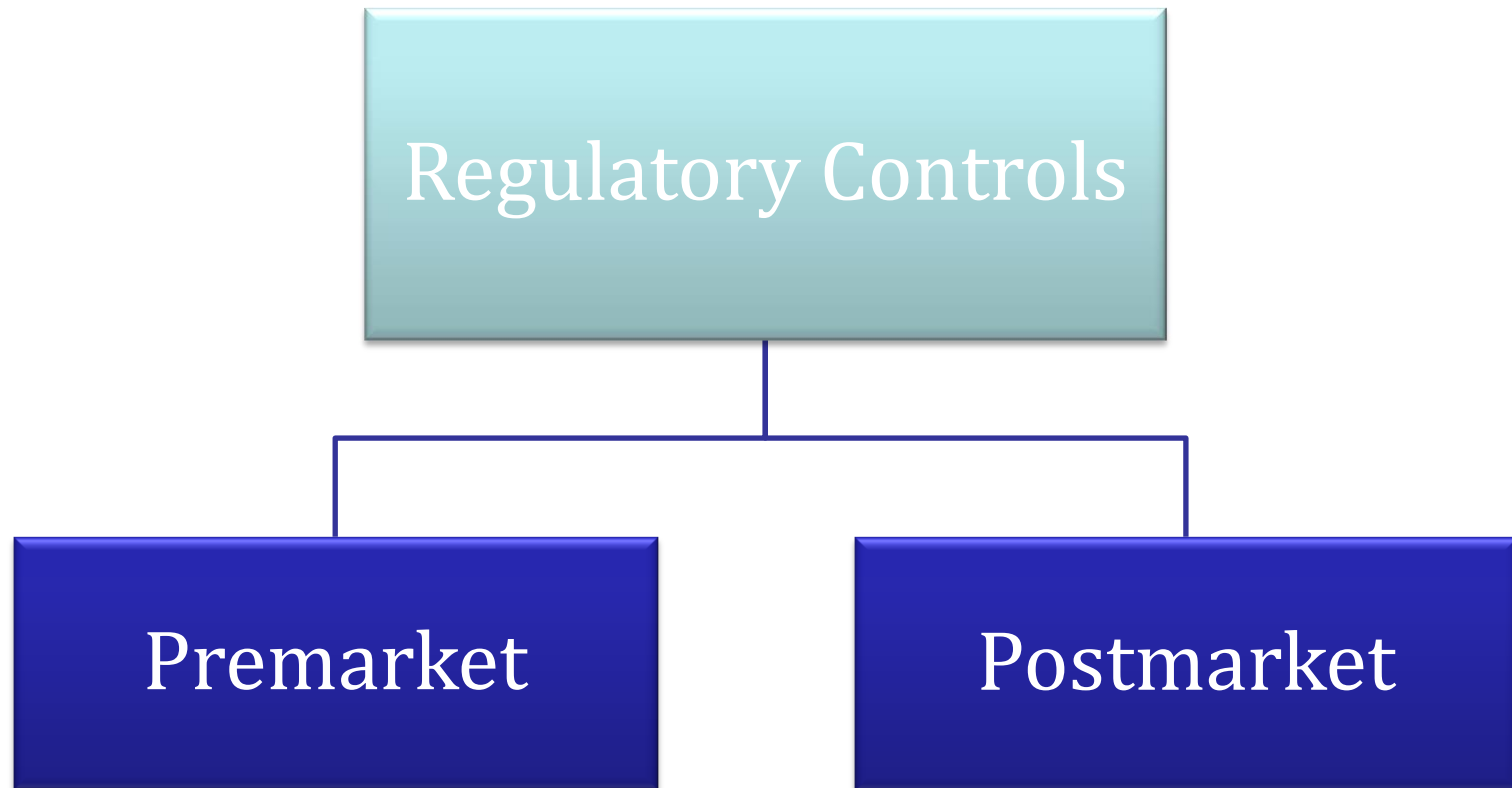
Rachel Goehe, PhD  
Kennita Riddick, MS

March 18, 2016

Docket No. FDA-2015-N-4462



# Marketing a Medical Device





## Objectives

- Overview of the regulatory requirements for IVDs intended for POC PT/INR devices.
  - Premarket
- Review past performance data criteria requirements in parallel with FDA's current way of thinking and considerations for future 510(k) submissions.

# Classification of IVD Devices

Class	Premarket Submission	Success Metric	Action/Decision
III	Premarket Approval (PMA)	Safety and Effectiveness	Approval
II	510(k) Premarket Notification (PMN)	Substantial Equivalence	Clearance
II (De Novo)	510(k)	Safety and Effectiveness	Granted
I	None (If exempt)		

## **21 CFR Part 807 Subpart E – Premarket Notification 510(k)**

If your device requires the submission of a Premarket Notification 510(k), you cannot commercially distribute the device until you receive a letter of substantial equivalence from FDA authorizing you to do so. A 510(k) must demonstrate that the device is substantially equivalent to one legally in commercial distribution in the United States: (1) before May 28, 1976; or (2) to a device that has been determined by FDA to be substantially equivalent.

## 21 CFR 864.7750 -- Prothrombin time test.

### 864 -- HEMATOLOGY AND PATHOLOGY DEVICES Subpart H--Hematology Kits and Packages

*(a) Identification.* A prothrombin time test is a device used as a general screening procedure for the detection of possible clotting factor deficiencies in the extrinsic coagulation pathway, which involves the reaction between coagulation factors III and VII, and to monitor patients receiving coumarin therapy (the administration of one of the coumarin anticoagulants in the treatment of venous thrombosis or pulmonary embolism).

*(b) Classification.* Class II (performance standards).

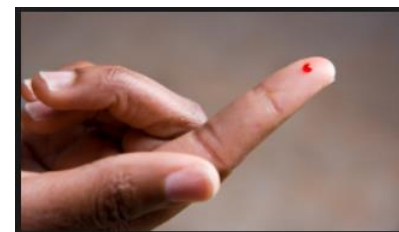
## Submission Elements Required for POC PT/INR Monitoring Systems

### **510(k) will include the following:**

- Intended Use/indications for use
- Device description
- Performance Specifications/Characteristics – analytical and clinical (method comparison) in the hands of professional and lay users
- Applicable software information
- Proposed labeling & training materials

# Review Elements of POC PT/INR Devices

- **Intended Use:** how and by whom the device is to be used
  - Measurement generated
  - Testing population
  - Specimen type(s)
  - Conditions for use/clinical setting/intended user
- **Indications for Use:** for what and for whom the device is to be used
  - Conditions or disease
  - Target population (e.g. age)



# POC PT/INR Testing Spectrum

## **Settings**

- Non-professional, home use self-testers
- Professional setting

## **Operators**

- Home user
- Family member caregiver
- Hospital lab
- Clinic
- Nursing home
- Emergency Department

## **Tests**

- Waived
- Moderately complex

## Performance characteristics: Analytical

1. Does the POC PT/INR measure the INR correctly?
2. How reliably? How precise?

- **Precision: repeatability/reproducibility**
  - Methods to establish the precision capabilities of the device and establishes performance claims.
  - Closeness of agreement between independent test/measurement results obtained under stipulated conditions.
- **Analytical specificity (interference)**
  - Physiological conditions, patient medications and patient specific sample attributes known to affect accuracy of results.
  - **Technology specific interferences are being considered as part of the 510(k) submission process for these devices.**
- **Traceability (to the International Reference Preparation)**



# Performance characteristics:

## Analytical

- **Quality control**

- Verifies device performance and can be built into the device, be external, or both.
- We have cleared PT/INR monitoring systems with only internal quality control or internal quality control and external quality control as an **option**.
- Critical since the device uses QC as a failure alert to help ensure “insignificant risk of an erroneous result.”
- **FDA is considering enhancing quality control requirements to potentially require external QC.**

- **Stability**

- Reagent
- Sample
- Test strip

- **Cleaning and disinfection**

## Performance characteristics: Clinical (method comparison)

1. Do the results from the test device correlate with the expected clinical presentation?
2. How reliably? How accurate?

- **Matrix considerations, claimed sample type(s)**

- Bridging study

- **Comparator**

- In the past, we have cleared POC PT/INR devices...
  - Candidate POC PT/INR vs. Predicate POC PT/INR
  - Candidate POC PT/INR vs. Plasma-based lab reference
- Currently, we clear POC PT/INR devices...
  - Candidate POC PT/INR vs. plasma-based lab reference and Candidate POC PT/INR vs. Predicate POC PT/INR

## Performance characteristics: Clinical (method comparison)

- **Analytical Measuring Range (AMR)**
  - Sponsors have used up to 10% contrived samples to assist in covering the proposed AMR.
  - We have allowed sponsors to only validate up to an INR of 4.5, even if the sponsor sought clearance for an AMR beyond an INR of 4.5 (e.g. INR of 8).
  - **FDA is considering having sponsors obtain all natural patients samples covering the entire proposed AMR.**
- **Three clinical sites representative of the intended use population(s)**
  - We have allowed sponsors to collect samples from limited POC settings which use PT/INR devices. For example, anticoagulation clinics.
  - **FDA is considering having sponsors fully support their intended use populations by testing a variety of POC settings.**

## Performance characteristics: Method Comparison

- **Acceptance criteria (established *a priori*)**
  - Question: Are the established limits reasonable to support validation of the proposed intended use while taking into consideration the therapeutic guidelines for warfarin?
- **ISO 17593:2007 not recognized**

### ISO 17593:2007

INR Range	Allowable Difference within <b>90%</b> of all results
< 2	± 0.5 INR
2.0 – 4.5	± 30%
≥ 4.5	No criteria set

### Proposal

INR Range	Allowable Difference within <b>95%</b> of all results
< 2	± 0.4 INR
> 2.0 – 3.5	± 20%
> 3.5 – 4.5	± 20%
>4.5 or greater	± 25%

# Device Labeling & Operator Training Materials

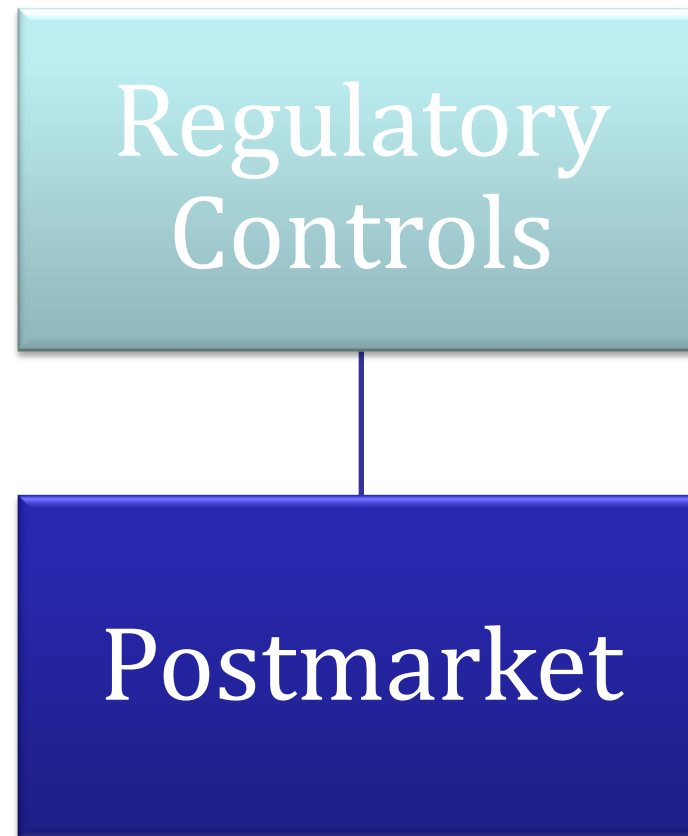
- **These materials should contain instructions for accurately using the POC PT/INR device and clear understanding of test performance and limitation.**
- **Waived POC PT/INR device are defined as 'simple' that have 'an insignificant risk of an erroneous result.'**
- **We are highly concerned with the labeling involved with these devices due to our postmarket analysis of MDRs which have demonstrated a high rate of operator error.**

# Feedback

**We encourage POC PT/INR device users, whether you are a home use self-tester, healthcare professional, caregiver, etc. to provide your experience and concerns by:**

- E-mailing our Branch at [PTINRFDA@fda.hhs.gov](mailto:PTINRFDA@fda.hhs.gov)
- Public comment via Docket Number: [FDA-2015-N-4462](https://www.fda.gov/oc/ohrt/docket/FDA-2015-N-4462)

# Marketing a Medical Device



# Objectives

- Provide an overview of the FDA's Medical Device Reporting (MDR) regulation requirements for POC PT/INR devices
- Explain the impact of adverse events related to POC PT/INR devices
- Describe data flow and reporting time frames for adverse events related to POC PT/INR devices



## Postmarket Challenges

- The performance of the meters provided for FDA clearance may not be reflective of the performance of the meters once they are commercially marketed.
  - Widening lot release criteria
  - Performance differences in a broad intended use population
  - Differences in international oversight
- Some companies do not accurately report.

# Quality System Regulation

## 21 CFR 820



# Analysis of FDA 483 Observations

Top 10 FDA 483 Observations
820.180-198 – Records
820.100 – CAPA
820.20-25 - QS Requirements
803 – MDRs
820.50 - Purchasing Controls
820.75 - Process Validation
820.70 - P&PC
820.90 - Non-Conforming Product
820.80-86 - Acceptance Activities
820.30(g) - Design Validation

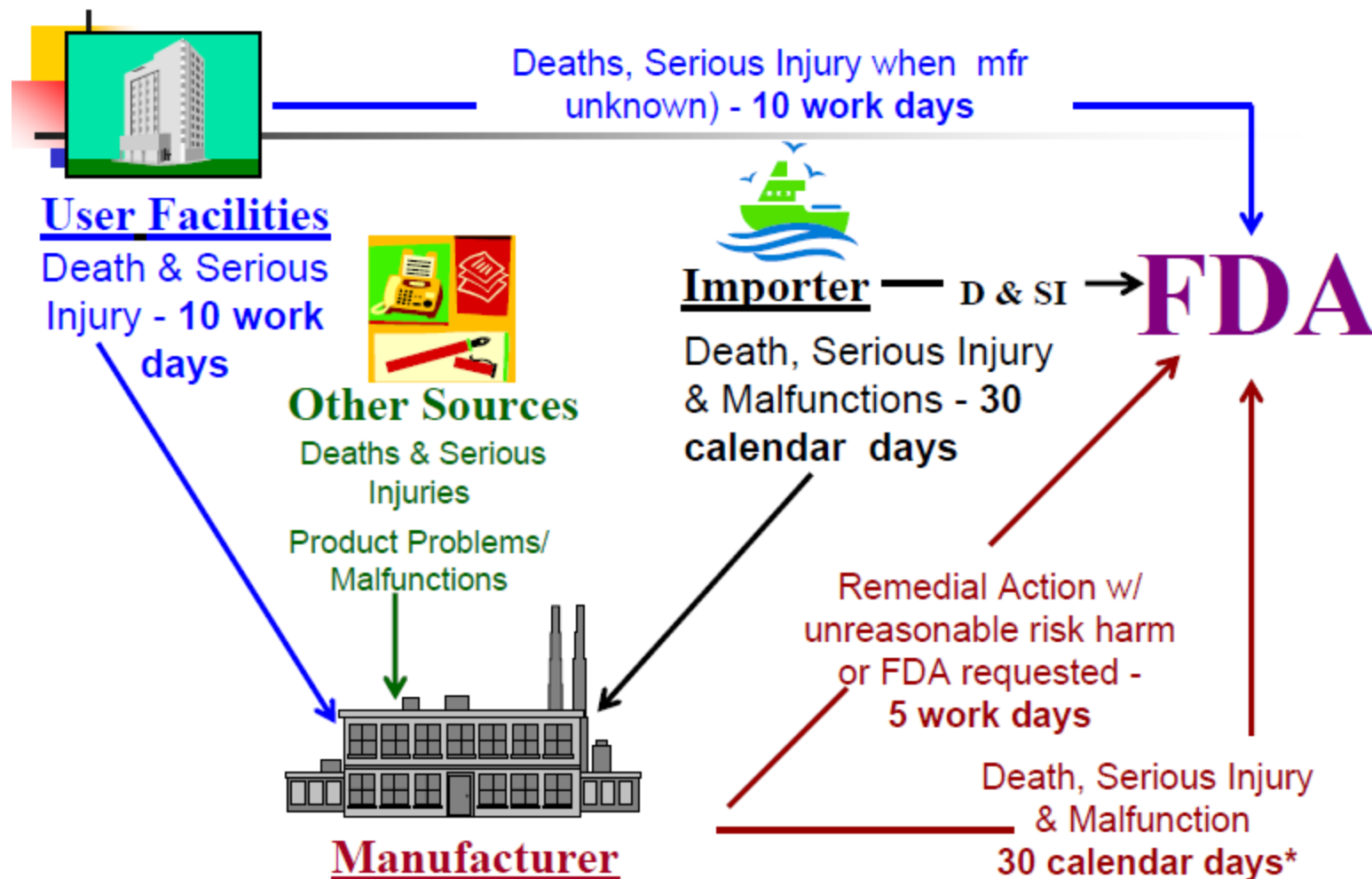
January 1, 2014 – Dec. 31, 2015

# Medical Device Reporting (MDR)

## 21 CFR 803

- Establishes requirements for medical device reporting for device user facilities, manufacturers, importers and distributors
- The goals are to ***detect*** and ***correct*** problems in a timely manner

# Data Flow and Reporting Timelines





## Adverse Events for Product Codes related to Hematology Prothrombin Time Test (GJS)

Event Type	MDR Count
Malfunction	3231
Injury	384
Death	18
Other	7
Invalid Data	5

January 1, 2014 – Dec. 31, 2015

# Hematology Prothrombin Time Test (GJS)

## Top 10 Device Problems

Top 10 Device Problems
Test Strip
Incorrect or inadequate test results
Incorrect or inadequate result
Low test results
High test results
Improper or incorrect procedure or method
Non-standard device or device component
Device displays error message
Device operates differently than expected
Improper device output

January 1, 2014 – Dec. 31, 2015

# Why Does the FDA Need Reports From User Facilities?

- To learn more about how marketed devices perform to identify and prevent adverse events when compliance issues occur.
  - Compliance Actions: (Inspections, Recalls, Safety Alerts or Notices)
- To identify devices that are not safe and effective for their intended use after approval or clearance for the market



# Point of Care User Facilities Defined

- Hospital
- Ambulatory Surgical Facility
- Outpatient Diagnostic Facility
- Outpatient Treatment Facility
- Nursing Home
- Home Use

# Mechanisms for Reporting Adverse Events

- Telephone: 1-800-FDA(332) 1088

- Online report form 3500

*(Patients and providers should utilize these forms for reporting adverse events)*

- Form FDA 3500 - Voluntary Reporting
- Form FDA 3500B - Voluntary Reporting for Consumers
- Form FDA 3500A - Mandatory Reporting

<http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm>

# FDA Request For Additional Information

- Why?
  - Regulation 21 CFR 803.15
- When?
  - FDA may request that you submit additional information if and when we determine that protection of the public health requires additional or clarifying information.

# Critical Information For Reporting Adverse Events

- Device brand
- Device model, lot , serial number
- Detailed narrative and evaluation
- Evaluation of returned devices
- Detailed investigation
- Explanation for conclusion
- Description of device function or feature that did not perform as intended
- Detailed corrections or planned actions

## Additional Resources

- Code of Federal Regulations 21 CFR Part 803:  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=803>
- Medical Device Reporting for Manufacturers:  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094529.htm>
- FDA Form 3500 and instructions:  
<http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm>
- FDA Website searching “MDR Reporting”

## Conclusion

- MDR Reporting is an essential mechanism for FDA surveillance
- Detailed information of adverse events are critical for assessment of post-market issues and development of pre-market evaluation
- Mandatory reporting requirements for manufacturers, importers, distributors and user facilities
- Voluntary reporting is encouraged

# *FDA CDRH Public Workshop: March 18, 2016*

## **Point of Care Prothrombin Time/International Normalized Ratio Devices for Monitoring Warfarin Therapy An Overview of Statistical Consideration**

***Meijuan Li, PhD, Branch Chief  
Diagnostic Statistics Branch 2  
Division of Biostatistics, CDRH/FDA***

# Types of PT/INR Diagnostic Devices

- Dichotomous tests with underlying continuous signal e.g. PT/INR value gives a yes/no or +/- result based on the cutoff defined as the threshold at which the device differentiates a positive from a negative test result
- Semi-quantitative tests e.g. with categorical output [no requirement for linearity]
- Quantitative test gives a measurement, or a numeric result within a specified range (measuring interval)

*This talk will focus on quantitative PT/INR tests*



# Validation of Quantitative PT/INR Diagnostic Devices

- Clinical Validation: Method comparison study
- Analytical validation (not comprehensive)
  - Precision (repeatability, intermediate precision, reproducibility)
  - Reference ranges
  - Sample type (capillary and venous whole blood)
  - Stability (of the test system and the measurand)
  - Interferences
  - .....

*This talk will use capillary blood as an example*

## Method Comparison Study Design-Capillary Blood

- Comparators:
  - Standard reference method: FDA cleared venous plasma based PT/INR assay
  - Predicate: FDA cleared whole blood (capillary whole blood) PT/INR assay
- Each patient is tested using the new device (capillary), the predicate (capillary), and the standard reference method (plasma derived from venous blood)
- Testing sites:
  - Several sites e.g. 3 sites representing the different types of sites that will use this device
  - Within each site, to the extent possible, the distribution of patient INR results covers the device measuring interval

## Method Comparison Study Design Cont.

- Patient samples:
  - Sufficient samples from the IU population, “evenly” distributed across the device’s entire measuring interval and sufficient samples within each of four INR ranges e.g.  $<2.0$ ,  $2.0 - 3.5$ ,  $3.5 - 4.5$ ,  $>4.5$
  - Sample size is calculated based on the study acceptance criteria and primary analysis e.g. regression analysis
- Collect information on patient’s disease state and any important variables

## Method Comparison Data Analysis

- Regression analysis:
  - regress the new device on reference method :
    - Slope ( $\beta_1$ ) and its 95% confidence interval
    - Intercept ( $\beta_0$ ) and its 95% confidence interval
    - Predicted bias at medical decision point(s)  $b_0$  and its 95% confidence interval
  - regress the predicate device on reference method and estimates
    - Slope ( $\alpha_1$ ) and its 95% confidence interval
    - Intercept ( $\alpha_0$ ) and its 95% confidence interval
    - Predicted bias at medical decision point(s)  $a_0$  and its 95% confidence interval
  - Compare: (1)  $\beta_1$  and  $\alpha_1$  (2)  $\beta_0$  and  $\alpha_0$  (3)  $b_0$  and  $a_0$
- Hypothesis of interest:
  - $H_0: -\delta \geq (\beta_0 - \alpha_0)$  or  $(\beta_0 - \alpha_0) \geq \delta$  or  $1 - \lambda \geq (\beta_1 - \alpha_1)$  or  $(\beta_1 - \alpha_1) \geq 1 + \lambda$
  - $H_a: -\delta < (\beta_0 - \alpha_0) < \delta$  and  $1 - \lambda < (\beta_1 - \alpha_1) < 1 + \lambda$
  - Note  $\lambda$  and  $\delta$  are equivalent margins which should be pre-specified clinically

# Additional Analysis

- Bland-Altman bias plots with limits of agreements (LOA)
  - a scatter plot of difference between the new test result and the reference standard result (y-axis) versus the mean of these two results (x-axis)]
  - a scatter plot of difference between the predicate result and the reference standard result (y-axis) versus the mean of these two results (x-axis)]
- Subgroup regression analysis and provide all performance estimates
  - below 2.0, between 2.0-3.5, 3.5 – 4.5, above 4.5
  - stratified by the following subgroups (1) site (2) patient population (3) any clinically relevant covariates or patient demographics
  - check data poolability

## Additional analysis

- For INR interval, provide the number (X) and percent of samples within the specified difference from the reference INR results. *Example*

Table 1. For reference INR <2.0

Within +/- 0.5 INR	Within +/- 1.0 INR	Within +/- 10 % INR	Within +/- 15% INR
X/Y (%) 95% CI	X/Y (%) 95% CI	X/Y (%) 95% CI	X/Y (%) 95% CI

Tables 2 and 3 . Separate tables for reference INR 2.0 -3.5 and >3.5

Within +/- 0.5 INR	Within +/- 10% INR	Within +/- 20% INR	Within +/- 30% INR
X/Y (%) 95% CI	X/Y (%) 95% CI	X/Y (%) 95% CI	X/Y (%) 95% CI

# Acceptance Criteria:

- The acceptance criteria on the intercept and slope for the method comparison study should be justified clinically and should be appropriate to demonstrate safety and effectiveness of your proposed device.

# Analytical Validation (not Comprehensive)

- Precision (repeatability, intermediate precision, reproducibility)
- Reference ranges
- Sample type (capillary and venous whole blood)
- Stability (of the test system and the measurand)
- Interferences
- .....

*This talk will discuss precision study*



# Precision

**Measurement precision:** the closeness of agreement between replicate measurements on the same object (e.g., sample) under specified testing conditions

- repeatability conditions (replicate measurements on the same or similar objects under the same or similar conditions)
- reproducibility conditions (replicate measurements on the same or similar objects using different operating conditions)
- some other set of intermediate conditions

*It is challenging for PT/INR assays to conduct a “typical” precision study recommended in EP5-A2 for capillary whole blood clinical samples*

# Precision Study Considerations

- Samples – both clinical samples and control material
  - The precision for each INR intervals should be evaluated
  - Clinical samples are recommended for “short term” precision
  - Control material can be used for “long term” precision
- Variables to be considered
  - Site, lot, day, run, replicate, machine, operator should be considered and designed properly in order to be estimated the variance component correctly
- Data analysis
  - Should respect study design e.g. nested vs. crossed

*This talk will discuss in house precision study for capillary blood clinical samples*

## **Example: In House Precision Study –Capillary Blood**

- To accommodate limited sample stability
- Allows least burdensome approach
- Evaluate: Operator, Instrument, and Lot variability in house precision, separately!
- Same study design will be used for operator, lot, and instrument, variability in house precision study

## Example: Study Design for Operator to Operator Variability-Capillary Blood

Site	In House		
Operator	A	B	C
Strip/Reagent Lot	Same		
Instrument	Same		
N=# of patients	2 fingers (preferably symmetrical) from each patient per operator x 3 operators = 6 fingers from each patients are tested by all 3 operators		

Three (3) operators, one (1) lot of the reagent, one (1) instrument;  
20 patients across AMR at in house site

INR Interval	INR Values	Subject Numbers	Total Data Points
Sub-therapeutic	<2.0	5	30
Therapeutic	2.0 to 3.5	5	30
Low supra-therapeutic	3.5 to 4.5	5	30
High supra-therapeutic	> 4.5	5	30

Data analysis using PT/INR values to estimate Sd and %CV

- Analyzing data for each INR interval separately
- Including sample (5), Operator (3), and run (2) in the model

# Summary

- The device's clinical and analytical validation have to be consistent to the device's indications for use
- The recommended validation studies will be device type dependent e.g. qualitative vs semi-quantitative or quantitative
- The acceptance criteria for both clinical and analytical validation studies need to be clinically justified and pre-specified prior to the initiation of validation studies
- Encourage the sponsor to discuss with FDA at the design stages

# Acknowledgement

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# PANEL SESSION

- Lea Carrington, MBA, MS, MT(ASCP)
- Randy Fenninger, JD
- Russell Higgins, MD, FCAP
- Paul T. Kocis, PharmD, RPh, CACP
- Frank LaDuca, PhD, FAHA
- Doug Patterson, MBA
- Rong Rong, MD, PhD
- Michael Streiff MD, FACP



# PANEL SESSION

## Topic 1

One source of error associated with POC PT/INR devices appears to be inadequate operator training or comprehension. FDA would like input on possible enhancements to existing operator training materials, or mechanisms to ensure demonstrated effective use of the POC PT/INR meters.

# PANEL SESSION

## Topic 2

To decrease the numbers of device malfunctions, FDA is considering enhancing quality control requirements. Currently quality control includes electronic and internal quality control on the test strips. Potential external quality controls being considered are 1) contrived control materials and 2) demonstration of testing proficiency at defined intervals by utilizing paired testing of the device and a plasma-based lab test. What other type of quality control(s) enhancements could significantly improve device control and functioning?



# PANEL SESSION

## Topic 3

CLSI document POCT14-A recognizes that results exceeding an INR of 5.0 generally have reduced trueness and precision in POC settings. In 510(k) applications submitted to FDA, the data above an INR of 5.0 are often collected from contrived specimens. FDA requests input on the usefulness for broad INR reportable ranges (e.g., 0.8 – 10 INR) in the setting of warfarin treatment monitoring and the feasibility of obtaining natural patient samples at the high INR range for device performance validation. FDA is considering whether manufacturers should validate the analytical measuring range with patient samples (not contrived).



**Docket No. FDA-2015-N-4462**

# PANEL SESSION

## Topic 4

INR results are used to monitor patients' response to warfarin, yet some of the currently marketed POC PT/INR devices also report PT results. PT results reported from these devices are usually not the conventional prothrombin time in seconds and are typically calculated using complex mathematical algorithms. FDA requests input on the usefulness of these calculated PT results in the setting of warfarin treatment monitoring.

# PANEL SESSION

## Topic 5

POC PT/INR devices have labeling that describes adjusting warfarin dose during home use of the device. FDA would like to discuss whether the appropriateness of a six-week stabilization window before prescription home use (patient self-testing) is an option. Are there cases where it would be appropriate to stabilize a patient with a POC PT/INR device versus a conventional plasma-based test? What special considerations should be assessed to enable POC PT/INR devices to be utilized to transition patients on and off of warfarin for medical procedures?



# PANEL SESSION

## Topic 6

POC PT/INR devices on the market today employ a wide range of technologies for clot detection. The inherent differences between various clot detecting technologies may affect the comparability between the INR results obtained from different PT/INR devices. FDA is requesting input on whether additional technology-specific interference studies should be part of our evaluation for POC PT/INR devices. If so, what additional interferences should be assessed for both direct and indirect clot detection technologies?

# PANEL SESSION

## Topic 7

What comparative devices should be used to evaluate the performance of a candidate POC PT/INR device in the method comparison study required for a premarket notification (510(k) submission). Please comment on the validation comparing a plasma-based laboratory method, a POC PT/INR predicate or both and what would be the clinically acceptable bias among the different INR ranges.

# PANEL SESSION

## Topic 7

### ISO 17593:2007

INR Range	Allowable Difference within <b>90%</b> of all results
< 2	$\pm 0.5$ INR
2.0 – 4.5	$\pm 30\%$
$\geq 4.5$	No criteria set

### FDA Proposal

INR Range	Allowable Difference within <b>95%</b> of all results
< 2	$\pm 0.4$ INR
> 2.0 – 3.5	$\pm 20\%$
> 3.5 – 4.5	$\pm 20\%$
>4.5 or greater	$\pm 25\%$

Docket No. FDA-2015-N-4462





# PANEL SESSION

## Q&A

**Docket No. FDA-2015-N-4462**



# BREAK

**Docket No. FDA-2015-N-4462**



## **Session 4**

# **Manufacturer Perspectives**

## **Moderator**

**Takesha Taylor-Bell, H(ASCP)**

*Scientific Reviewer*

*Hematology Branch*

*Division of Immunology and Hematology Devices*

*OIR/CDRH/FDA*



# Assessing Accuracy for PT/INR Testing using POC Devices

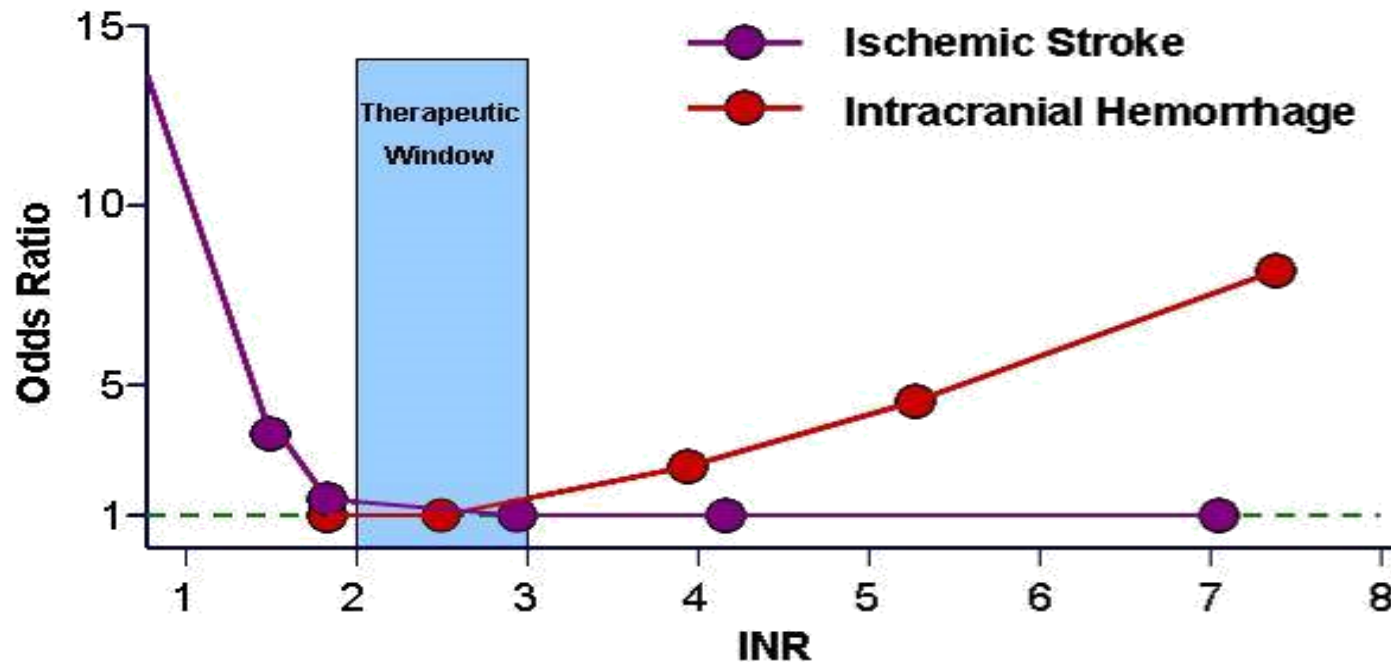
FDA Workshop for POCT – PT/INR for Monitoring Warfarin Therapy  
March 18, 2016

Frank M. LaDuca, Ph.D., FAHA  
CSO, Accriva Diagnostic  
CLSI, POCT Consensus Committee

# Agenda and Objectives

- PT/INR and Warfarin Anticoagulation Management
  - Tight Therapeutic Window
  - Benefits of PT/INR Monitoring
- Considerations for POC - PT/INR Systems
  - Accriva PT/INR System Features
- Performance Criteria & Clinical Validation
  - Laboratory System PT/INR Agreement
  - POCT System PT/INR Agreement
  - Acceptance Criteria (Limits of Agreement) in Comparative Studies for POCT
- Consensus Standards for Acceptance Criteria and Clinical Agreement

# PT/INR and Patient Management



Hylek. *Ann Intern Med.* 1994;120:897-902.

Hylek. *N Engl J Med.* 1996;335:540-546.

## Goal is to Maintain a Tight Therapeutic Range

- Prosthetic Heart Valves 2.5 - 3.5 INR
- All other indications (A-Fib, DVT) 2.0 - 3.0 INR
- Practical Considerations

242 — A-Fib complications increase from 4% at age 65 to >15% at age 75

# The Benefits of Access to PT/INR Monitoring

- Increased Testing Frequency Yields Increased Time in Therapeutic Range (TTR) <sup>a</sup>
- Direct Relationship of increased TTR to reduced Event Rate <sup>a</sup>
  - Evidence based literature demonstrates association of PT/INR test frequency, improved TTR and reduced event rate <sup>a</sup>
- INR is not a perfect system, but effective
  - “Despite [INR] variation between different test systems, the Prothrombin Time and its derivative, the INR has been shown to correlate with important outcomes in multiple clinical trials” <sup>b</sup>
- INR testing yields Improved patient management
  - “The INR method is not perfect in correcting for differences among different laboratories utilizing different thromboplastin reagents, but it does reduce the variation among different laboratories and provides clinically useful results” <sup>a</sup>

<sup>a</sup> *Samsa G, Matcher D; Relationship between test frequency and outcomes of anticoagulation; Literature review....J Thromb Thrombolysis, 2000*

<sup>b</sup> *Garcia D et al; Delivery of Optimized Anticoagulant Therapy: Consensus Statement from the Anticoagulation Forum. Ann Pharmacology, 2008*

# Considerations for POC – PT/INR Systems

- Operator Training & Competency
- Patient Education Materials
- Biohazard Control
- Quality Control & Quality Assurance – Ensure System Stability
  - External QC – Quantitative (Required)
  - Internal QC – Quantitative or semi- quantitative (Optional for Professional Use)
- Data Management (storage and transmittance to medical record)
- Accuracy
  - Comparison to the Reference INR (correlation and bias);
  - Calibrated to the WHO Tilt-Tube method and rTF material
- Precision – repeatability of testing
- Clinical (Limits of) Agreement – ensure equivalence of patient management decisions from INR test results, recognizing known INR system variance

## ITC Systems



Signature 1994, 2004



ProTime 1995, 2006

## Accriva System



InRhythm 2016 [pre-510(k)]





# Accriva POCT PT/INR Systems

System	Hemochron <sup>®</sup> Sig/Elite	ProTime <sup>®</sup>	InRhythm <sup>®</sup>
<b>FDA status</b>	510(k) 1994, 2004	510(k) 1995, 2006	Pre-510(k)
<b>Clot Detection Technology</b>	Mechanical clot based (fibrin)	Mechanical clot based (fibrin)	Mechanical clot based (fibrin)
<b>End Point Detection</b>	Blood movement measured by LED	Blood movement measured by LED	Blood movement measured by viscosity (pressure)
<b>CLIA Category</b>	Moderately Complex	Moderately Complex & CLIA Waived	Moderately Complex & CLIA Waived (propose)
<b>Thromboplastin reagent</b>	Calibrated rabbit brain	Recombinant TF	Recombinant TF
<b>Calibration</b>	Secondary Reference tied to WHO standard	Secondary Reference tied to WHO standard	Secondary Reference tied to WHO standard Direct ISI measured against WHO standard
<b>Quality Control (note <sup>a</sup>)</b>	External (2 level)	Internal and External (2 level)	Internal and External (2 level)

<sup>a</sup> External and Internal QC is a functional clotting test (fibrin based) to assess reagent and total system integrity

# Lab Based PT/INR (Dis)Agreement Reality

Source	Average INR	INR Variability Across Systems	Observed % Variance
Jacobson	2.0	$\pm 0.4$	<b>20 %</b>
1999/2008	3.0	$\pm 0.8$	<b>30 %</b>
	4.0	$\pm 1.2$	<b>30 %</b>
McGlasson (2003)	3.0 to 4.0	1.04 to 2.88	<b>32 % to 81%</b>
(7 systems)	4.0 to 5.0	1.43 to 3.21	<b>33 % to 61 %</b>
CAP Proficiency 2005	2.0	1.5 to 2.7	<b>60 %</b>
(Jacobson 2008)	4.0	2.2 to 6.9	<b>117 %</b>
CAP Proficiency 2012	2.75 (3 trials)	2.46 to 3.34	<b>32 %</b>
(26 Lab Systems	4.98 (1 trial)	4.05 to 7.14	<b>62 %</b>
4890 Reports)	5.6 (2 trials)	4.51 to 7.82	<b>59 %</b>

Jacobson A et. al. Significant variation in the reporting of PT results despite utilization of the INR method of reporting. Circulation. 1999

McGlasson D. Laboratory Variables that may affect test results in PT/INR. Lab Med 2003

Jacobson A. Warfarin monitoring: POC INR testing limitations and interpretation of the PT. J Thomb Thrombolysis 2008

# Published Studies Showing Reliable POCT – PT/INR

Study	Comparison Results	Conclusion
Kaatz 1995	Split sample analysis – systems vs. tilt tube 4 lab systems; 2 POC systems	With regards to correlation, the 2 POC systems performed in the middle of the 6 systems tested; i.e., 2 lab systems better, 2 lab systems worse correlation
Bussey 1997	Comparison of 2 lab systems and 2 POC systems	Lab systems indicated erroneous dosage changes when POC did not.
Murray et al 1999	Comparison of 3 POCT systems to a reference lab	All 3 POCT systems produced acceptable and reliable INR results within the therapeutic range
Hobbs et al 1999	405 split sample analysis across lab systems and POC	POCT INR results as reliable as lab INR results
Ryan et al 2008	673 paired samples	Good agreement between 2.0 and 3.5 (87% agreement). POCT is reliable.
Solvik et al 2010	Comparison of 1 lab system and 3 POC	Mean difference between systems ranged from 1 to 14% across therapeutic range. No difference between lab and POCT
Murray and Greaves 2010	Literature Analysis	A difference exists between statistical and clinical significance when considering INR. POCT systems deliver accurate clinical decisions

# POCT - PT/INR Agreement

## (POCT 14A Consensus Candidate Limits)

Source	INR Range	Agreement Limits
CLSI POCT 14A	1.0 to 2.5	$\pm 0.4$
CLSI POCT 14A	2.6 to 3.5	$\pm 0.7$
Literature	3.6 to 5.0	$\pm 0.9$
Literature	Above 5.0	$\pm 1.2$

### Supportive Literature Citations

Lassen JF et al. INR for PT in patients .....Critical difference and probability of significant change in consecutive measurements, *Clin Chem*. 1995.

Oral Anticoagulation Monitoring Study Group. POC PT measurement for professional and patient self-testing use, *Am J Clin Path*. 2001.

Hobbs et al. Is the INR reliable? A trial .....in hospital laboratory and primary care settings. *J Clin Pathol*, 1999.

Jacobson A. Warfarin monitoring: POC INR limitations and interpretations. *J Thromb Thrombolysis*, 2008.

Ansell J et al. Pharmacology and management of Vit K: Am Coll Chest Physicians Evidence Based Clinical Practice Guidelines. CHEST 2008.

# Acceptance and Agreement Limits (LOA)

## Level 1 Evaluation (Correlation) Requirements

Slope = 1.0 (95% confidence limits); y-intercept = 0.0 (95% confidence Limits)  
INR Bias estimates (at clinical decision limits)

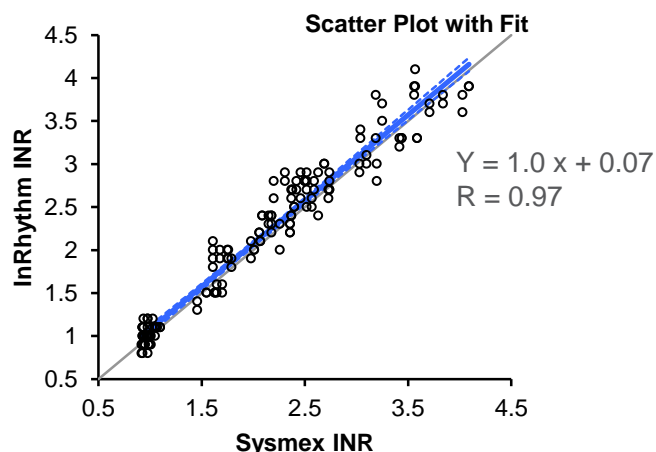
Target INR	POCT 14A Agreement	Agree within 0.5 INR	10 % Agreement Range	20 % Agreement Range
1.6	1.2 to 2.0	1.1 to 2.1	1.4 to 1.8	1.3 to 1.9
2.6	1.9 to 3.3	2.1 to 3.1	2.3 to 2.9	2.1 to 3.1
3.6	2.7 to 4.5	3.1 to 4.1	3.2 to 4.0	2.9 to 4.3
4.6	3.7 to 5.5	4.1 to 5.1	4.1 to 5.1	3.7 to 5.5
5.6	4.4 to 6.8	5.1 to 6.1	5.0 to 6.2	4.5 to 6.7
6.6	5.4 to 7.8	6.1 to 7.1	5.9 to 7.3	5.3 to 7.9

## Conclusion

- Pre-established acceptance criteria based on identified source dramatically impacts perceived system equivalence to the reference standard.
- Literature cited agreement limits (referenced in POCT 14A) represent best clinician supported requirements.
- POCT 14A standards and 20% limits yield equivalent LOA results

# Correlation & LOA assessment - Comparison

Typical Correlation Study  
InRhythm and Reference Standard  
N = 158 specimens from VKA



POCT equivalence based on correlation linear fit (solid line) with 95% confidence limits (dashed bands) and correlation statistic

InRhythm LOA (POCT 14A) against  
Reference

Comparative Study (N= 347 Specimens from VKA Patients)  
Agreement with Reference Standard (Sysmex-Innovin) INR

INR range	Acceptable limit (INR)	(N) samples (12 lots)	% within acceptable limit
up to 2.5	0.4	249	99%
2.6 - 3.5	0.7	88	100%
> 3.5	0.9	10	100%

InRhythm LOA (20%) against Reference

Comparative Study (N=123 Specimens from VKA Patients)  
Agreement with Reference Standard (Sysmex - Innovin) INR

(N=123)	(N)		Percent (%)	
	Ref POCT	InRhythm	Ref POCT	InRhythm
LOA (%)				
<10%	77	81	62.6	65.9
10-20%	40	33	32.5	26.8
20-30%	5	7	4.1	5.7
>30%	1	2	0.8	1.6

# POCT 14A - Consensus Standard

- CLSI POCT 14A Revision Proposal Submitted
  - M Zucker (Independent); C Dollins (FDA); F LaDuca (Industry)
- Define objective comparison criteria and acceptance criteria based on literature
  - Correlation slope, intercept and bias estimates
- Evidence based medicine documentation provides basis of consensus standard for limits of agreement (LOA)
- Will leverage general POCT testing considerations from other CLSI documents, e.g., selection criteria, etc.
- Consensus Documents are designed to provide common approach to PT/INR assessment criteria across healthcare provider, manufacturer and FDA for system adaptation.
- POCT 14A LOA criteria “tighter” than ISO 17593:2007 (PST standard – not FDA recognized) which provides for 30% agreement limits for INR of 2.0 to 4.5 (compared to Reference INR)

*CLSI POCT 14A - Point-of-Care Monitoring of Anticoagulation Therapy*

# Summary and Conclusions

## POCT PT/INR Systems and Warfarin Management

- POCT PT/INR provides ready access to frequent monitoring of PT/INR. Frequent PT/INR monitoring promotes TTR and improved care (Slide 4).
- POCT (PT/INR) must meet essential requirements to ensure safety and efficacy (slides 5, 6)
  - performance acceptance criteria
  - Quality Control
  - Data management
  - Quality Assurance and Training

## PT/INR Precision, Accuracy and Agreement

- Lab PT/INR has known large variance across lab systems (slide 7).
- Published studies show POCT PT/INR is reliable (slide 8, 9).
- POCT PT/INR clinical agreement criteria (LOA) should parallel literature (evidence) based requirements (slides 9, 10, 11).





Knowing now matters.™



## Point of Care Prothrombin Time/International Normalized Ratio Devices for Monitoring Warfarin Therapy

FDA Public Workshop

Considerations for POC INR Performance

March 18, 2016      Rick San George, Ph.D.



# Overview of Device Technology

## INRatio™ System: Test Strip and Monitor

- Used for the quantitative measurement of PT/INR in fresh, capillary whole blood
- Professional use
- Patient self-test use
- For monitoring therapy using warfarin and other oral anticoagulants
- Utilizes recombinant human thromboplastin
- Clot detection using impedance measurements
- 0.7 to 7.5 INR measurement range



# R&D to Assess and Improve Accuracy

## Selection of thromboplastin reagent

- Human recombinant, rabbit brain, ISI
- Formulation – tissue factor, phospholipids, salts, stabilizers, etc.
- Application – volume, location, drying, etc.

## Development of calibration process

- Selection of in-house venous plasma reference INR method
  - Selection based on thromboplastin, ISI and traceability to WHO
  - Development of test process using fresh fingerstick whole blood samples and venous plasma from patients taking warfarin and from non-warfarin normal individuals.
  - Verify traceability to WHO tilt tube primary reference method
    - Comparison of fingerstick INR results and plasma reference method INR results to tilt-tube method
    - Per WHO TRS 889 guidelines
    - 60 patient samples, 20 normal samples
    - Tilt-tube method conducted by WHO certified laboratory and using WHO international reference preparation samples and thromboplastin reagents.

## External multi-site evaluation of accuracy by comparison of POC INR results to laboratory plasma reference INR method

- POC tests performed by professional users and patient self-test (PST) users



# Interferences

## Hematocrit

- Limited to samples in 30-55% hematocrit range

**Lupus and antiphospholipid syndrome (APS) may falsely prolong INR.**

## Heparin

- INR is prolonged in presence of heparin, unfractionated or low molecular weight
- Reagents containing heparin neutralizing agents can reduce interference from heparin
- Manufacturers have historically evaluated interference by testing blood samples
  - spiked with heparin
  - from warfarin patients injected with heparin
  - from patients bridging from heparin to warfarin

# Criteria for assessing accuracy and precision in comparison to plasma-based laboratory tests



# Device Accuracy and Precision

Methods of evaluation and acceptance criteria (compared to plasma-based laboratory tests)

## Accuracy - professional

**External multi-site (4) evaluation of accuracy by comparison of POC INR results to laboratory plasma reference INR method**

- POC tests performed by professional users
- 288 patient samples (263 warfarin, 25 non-warfarin)
- Deming regression, Bland-Altman analysis, total error assessment
- Acceptance criteria:
  - System accuracy per ISO 17953 (2007): allowable differences: >90% of differences within  $\pm 30\%$  for INR 2-4.5 and within  $\pm 0.5$  for INR <2. Mean bias  $\leq 0.3$  INR units for INR interval of 2-4.5.

**Calibration and QC release of newly manufactured test strips**

- Fresh capillary whole blood INR comparison to venous plasma laboratory reference method INR results
  - Samples from patients taking warfarin and from non-warfarin individuals
- Acceptance criteria
  - Tighter than system accuracy criteria per ISO 17953 (2007)



# Device Accuracy and Precision

## Methods of evaluation and acceptance criteria

### Precision - professional

#### External multi-site (4) evaluation comparison of POC INR results to laboratory plasma reference INR results

- 287 fingerstick patient samples (263 warfarin, 24 non-warfarin) tested in duplicate
- Duplicate %CV calculations based on duplicate fingerstick INR results
  - INR intervals of <2, 2.0-3.0, 3.1-4.5, >4.5, 2.0-4.5
- Acceptance criteria:
  - Sufficient to achieve system accuracy per ISO 17953 (2007): allowable differences: >90% of differences within  $\pm 30\%$  for INR 2-4.5 and within  $\pm 0.5$  for INR <2.

#### Calibration and QC release of newly manufactured test strips

- Fresh capillary whole blood INR comparison to venous plasma laboratory reference method INR results
  - Samples from patients taking warfarin and from non-warfarin individuals
- Acceptance criteria
  - %CV needs to be below specifications for samples from patients taking warfarin and non-warfarin individuals



# Device Accuracy and Precision

Methods of evaluation and acceptance criteria (compared to plasma-based laboratory tests)

## Accuracy – PST Lay User

**External multi-site (4) evaluation of accuracy by comparison of PST lay user POC INR results to health care professional (HCP) POC results and to laboratory plasma reference INR method**

- 106 warfarin patient study subjects
  - Diverse educational backgrounds
- Training visit and study visits at 4 weeks and 8 weeks
- Deming regression, Bland-Altman analysis, total error assessment
  - PST vs. HCP, PST vs. lab, HCP vs. lab for data at weeks 4 and 8
- Acceptance criteria:
  - System accuracy per ISO 17953 (2007): allowable differences: >90% of differences within  $\pm 30\%$  for INR 2-4.5 and within  $\pm 0.5$  for INR <2. Mean bias  $\leq 0.3$  INR units for INR interval of 2-4.5.
- Error rates for PST and HCP users
- User evaluation questionnaire
  - Collecting sample, applying sample, reading display, operating system, understanding training and labeling, confirming system performance





# Device Accuracy and Precision

## Methods of evaluation and acceptance criteria

### Precision – PST Lay User

#### External multi-site (4) evaluation comparing PST lay user fingerstick INR results to HCP fingerstick INR results

- 106 warfarin patient study subjects
  - Diverse educational backgrounds
- Training visit and study visits at 4 weeks and 8 weeks
- Duplicate %CV calculations based on duplicate fingerstick INR results
  - PST and HCP for data at weeks 4 and 8
  - INR intervals of <2, 2.0-3.0, 3.1-4.5, >4.5, 2.0-4.5
- Acceptance criteria:
  - Sufficient to achieve system accuracy per ISO 17953 (2007): allowable differences: >90% of differences within  $\pm 30\%$  for INR 2-4.5 and within  $\pm 0.5$  for INR <2.



# Sources of Error: Laboratory and POC

## Pre-Analytical Sources of Error

### Laboratory

- Fill volume of blood collection
- Time before centrifugation of venous blood
- Time before testing venous plasma
- On-board age of reagent
- On-board age of reagent calibration
- Stability of calibrator
- Shelf-life of reagent

### Point of Care

- Poor fingerstick
- Sample application
- Time before sample application
- Calibration code



# Sources of Error: Laboratory and POC

## Analytical Sources of Error

### Laboratory

- Imprecision within-run
- Inaccuracy - ISI assignment

### Point of Care

- Imprecision test strip-to-test strip
- Inaccuracy - ISI assignment
- Test strip shelf life

## Variability Among Laboratory Methods

- ISI doesn't fully standardize INR methods
- Lab methods differ among each other
- Differences are greatest in high INR range
- POC methods agree with selected lab methods
- POC methods cannot agree with all lab methods



# Device Accuracy and Precision

## Variability Among Laboratory Methods

### CAP 2014 CGL-A

- Analyte: INR
- Target Value: Peer Group
- Evaluation Criteria:  $\pm 20\%$

## Low INR

International Normalized Ratio							
REAGENT/INSTRUMENT	NO. LABS	MEAN	S.D.	C.V.	MEDIAN	LOW VALUE	HIGH VALUE
CGL-05	25	1.24	0.09	7.4	1.2	1.1	1.5
	1013	1.22	0.05	4.5	1.2	1.1	1.4
	117	1.23	0.05	4.4	1.2	1.1	1.3
	286	1.26	0.06	4.6	1.3	1.1	1.4
	5	-	-	-	1.2	1.2	1.4
	65	1.24	0.05	4.0	1.2	1.2	1.3
	21	1.24	0.06	4.8	1.2	1.1	1.3
	48	1.38	0.10	7.3	1.4	1.2	1.6
	59	1.40	0.09	6.3	1.4	1.2	1.6
	15	1.28	0.12	9.4	1.3	1.1	1.5
	14	1.21	0.05	3.9	1.2	1.1	1.3
	5	-	-	-	1.3	1.2	1.4
	293	1.28	0.07	5.7	1.3	1.1	1.6
	52	1.28	0.05	4.2	1.3	1.2	1.4
	679	1.25	0.06	4.8	1.2	1.1	1.4
	5	-	-	-	1.3	1.2	1.3
	15	1.28	0.04	3.2	1.3	1.2	1.3
	5	-	-	-	1.3	1.2	1.4
	231	1.36	0.06	4.7	1.4	1.2	1.5
	1558	1.31	0.05	4.0	1.3	1.2	1.4
	6	-	-	-	1.3	1.2	1.3
	27	1.33	0.05	4.0	1.3	1.2	1.4
	5	-	-	-	1.2	1.1	1.3
	63	1.12	0.07	5.9	1.1	1.0	1.2
	6	-	-	-	1.2	1.0	1.2
	23	1.36	0.08	6.2	1.4	1.2	1.5
	20	1.25	0.07	5.5	1.2	1.2	1.4

◆=MECHANICAL



# Device Accuracy and Precision

## Variability Among Laboratory Methods

### CAP 2014 CGL-A

- Analyte: INR
- Target Value: Peer Group
- Evaluation Criteria:  $\pm 20\%$

## Mid INR

International Normalized Ratio							
REAGENT/INSTRUMENT	NO. LABS	MEAN	S.D.	C.V.	MEDIAN	LOW VALUE	HIGH VALUE
CGL-02	25	3.25	0.22	6.8	3.2	2.9	3.7
	1011	2.95	0.16	5.3	2.9	2.5	3.4
	117	3.02	0.17	5.6	3.0	2.6	3.4
	282	2.97	0.13	4.5	3.0	2.6	3.4
	5	-	-	-	2.9	2.8	3.1
	63	2.76	0.10	3.7	2.8	2.6	3.0
	21	2.88	0.07	2.6	2.9	2.8	3.0
	46	2.71	0.23	8.5	2.7	2.3	3.4
	60	2.72	0.18	6.6	2.7	2.3	3.1
	15	2.79	0.24	8.5	2.8	2.4	3.2
	14	2.39	0.12	5.2	2.4	2.2	2.5
	5	-	-	-	2.7	2.5	2.8
	293	2.75	0.16	5.9	2.8	2.2	3.3
	51	2.82	0.12	4.4	2.8	2.6	3.0
	676	2.78	0.16	5.8	2.8	2.3	3.2
	5	-	-	-	2.9	2.7	3.1
	15	2.42	0.13	5.5	2.4	2.2	2.6
	5	-	-	-	2.5	2.4	2.6
	233	2.56	0.13	4.9	2.6	2.2	2.9
	1566	2.46	0.13	5.1	2.5	2.1	2.8
	6	-	-	-	2.4	2.3	2.6
	28	2.67	0.15	5.8	2.7	2.3	3.0
	5	-	-	-	2.7	2.4	2.7
	61	2.68	0.21	7.8	2.7	2.3	3.2
	7	-	-	-	2.6	2.5	2.9
	23	2.66	0.17	6.4	2.6	2.4	3.0
	20	2.54	0.19	7.5	2.5	2.2	2.9

◆=MECHANICAL



# Device Accuracy and Precision

## Variability Among Laboratory Methods

### CAP 2014 CGL-A

- Analyte: INR
- Target Value: Peer Group
- Evaluation Criteria:  $\pm 20\%$

## High INR

International Normalized Ratio							
REAGENT/INSTRUMENT	NO. LABS	MEAN	S.D.	C.V.	MEDIAN	LOW VALUE	HIGH VALUE
CGL-04	25	6.94	0.61	8.7	7.0	5.6	7.8
	1010	5.98	0.40	6.7	6.0	4.9	7.1
	114	6.17	0.42	6.8	6.1	5.2	7.4
	282	5.90	0.34	5.7	5.9	5.0	6.8
	5	-	-	-	5.8	5.7	6.3
	65	5.05	0.23	4.5	5.0	4.6	5.7
	22	5.21	0.29	5.6	5.2	4.5	6.0
	45	5.52	0.58	10.5	5.4	4.3	6.9
	59	5.48	0.44	8.1	5.5	4.3	6.4
	15	5.75	0.41	7.2	5.7	5.1	6.4
	14	4.00	0.22	5.5	4.0	3.6	4.3
	5	-	-	-	5.1	4.2	5.3
	293	4.81	0.29	6.1	4.8	4.0	5.7
	50	5.00	0.25	5.0	5.0	4.3	5.7
	675	4.93	0.31	6.2	4.9	4.0	5.8
	5	-	-	-	5.4	5.4	5.4
	15	3.96	0.24	6.1	3.9	3.6	4.4
	5	-	-	-	4.1	3.9	4.3
	229	4.25	0.22	5.1	4.2	3.6	4.8
	1564	4.13	0.26	6.3	4.1	3.2	5.0
	6	-	-	-	3.9	3.8	4.2
	26	4.69	0.34	7.3	4.7	3.8	5.4
	5	-	-	-	4.6	4.1	4.8
	60	4.64	0.48	10.3	4.7	3.6	5.9
	7	-	-	-	4.5	4.2	5.0
	23	4.90	0.41	8.4	5.0	3.9	5.6
	19	4.43	0.41	9.2	4.3	3.9	5.2

◆=MECHANICAL



# Device Accuracy and Precision

## Variability Among Sample Matrices

- Capillary vs. venous whole blood bias
- Whole blood vs. plasma bias; hematocrit effects
- Plasma incompatibility
- Proficiency test materials

## Need for Contrived Samples for Product Development and Validation

- Reportable range 0.8 to 7.5 INR
  - User requirement
- Difficult to obtain fresh fingerstick samples at high INR
  - 9 out of 288 samples in clinical study had INR >5, or about 3%
- Calibration process may not have many samples with INR >5
- Certified plasmas not typically available at high INR
- May not be possible to use banked high INR plasma samples
- Need to assess accuracy and other aspects of performance at high INR

# Benefits/Risks of POC vs. Laboratory

## Benefits of POC vs. Laboratory

- Time to result
- Communication with patient and dosage adjustments
- Patient self-testing
- Potential for higher frequency of testing
- Potential for higher time in therapeutic range (STABLE study) and better outcomes
- Good option for some patients who live far from clinic

## Risks of POC vs. Laboratory

- Possible systematic bias compared to laboratory
  - Bias is variable depending on local laboratory method
- Possibly higher imprecision & total error
- Hematocrit effects
- Performance at high INR
- Lay user errors



# Thank you



# **FDA Regulation of Prothrombin Time/International Normalized Ratio (PT/INR) Devices for Point of Care Testing (POCT)**

March 18, 2016

Douglas Patterson  
Founder & CEO CoaguSense, Inc.



# POC PT/INR System Design Challenge

## The POC PT/INR Test System Design Challenge-

- PT/INR test is a key clinical management tool with significant implications
- Need to measure a process, not quantify a molecule
- Many secondary detection technologies (photometric, fluorescent and amperometric) have failed
  - Poor precision
  - Susceptibility to interfering substances and Hemoglobin and Hematocrit levels
- Must be able to compensate for H&H levels
  - 10-50% of patient population is anemic<sup>1</sup>
  - or be accompanied by a hematocrit test
- Must have ability to run plasma controls/calibrants to confirm system performance

# POC PT/INR System Design Challenge

## Importance of Hematocrit

- Hematocrit values<sup>1</sup> and differences in clot detection mechanisms<sup>2</sup> are cited as top potential sources of inaccuracy between whole blood (WB) and plasma assays
- The impact is significant, especially in samples with high INRs
- Sickest patients with high/low hematocrit values most at risk for a clinically significant error
  - particularly if they have INRs more than 3.0.<sup>3</sup>
- A 10% hematocrit variance at critical INR values can change how a patient will be managed

Brand (A) PT/INR System User Manual: “A hematocrit (percentage of blood that is red blood cells) that is higher or lower than the validated operating range of the system can cause an inaccurate result. Refer to the test strip package insert for more information. Verification of the patient’s hematocrit will help ensure the reliability of results obtained with the PT monitor.”

- Can’t rely on POC/PST user to perform check hematocrit prior to INR test

1. Gosselin R, Owings JT, White RH, et al. A comparison of point-of-care instruments designed for monitoring oral anticoagulation with standard laboratory methods. *Thromb Haemost.* 2000;83:698–703.

2. Poller L, Keown M, Chauhan N, et al. Reliability of international normalised ratios from two point of care test systems: comparison with conventional methods. *BMJ.* 2003;327:30. doi:10.1136/bmj.327.7405.30.

3. Timothy K. Amukele, MD, PhD, Chris Ferrell, MT(ASCP) and Wayne L. Chandler, MD Comparison of plasma with whole blood prothrombin time and fibrinogen on the same instrument. *American Journal of Clinical Pathology*, 133, 550-556.

4. Van Den Besselaar AMHP, Witteveen E, van der Meer FJM, Influence of hematocrit on International Normalised ratio (INR) difference between whole blood point of care monitor and reference prothrombin time in plasma. *Thromb Haemost* 2008; 100:1181-1184 272

# POC PT/INR System Design Challenge

## Simplifying the Gold Standard- The Fibrometer

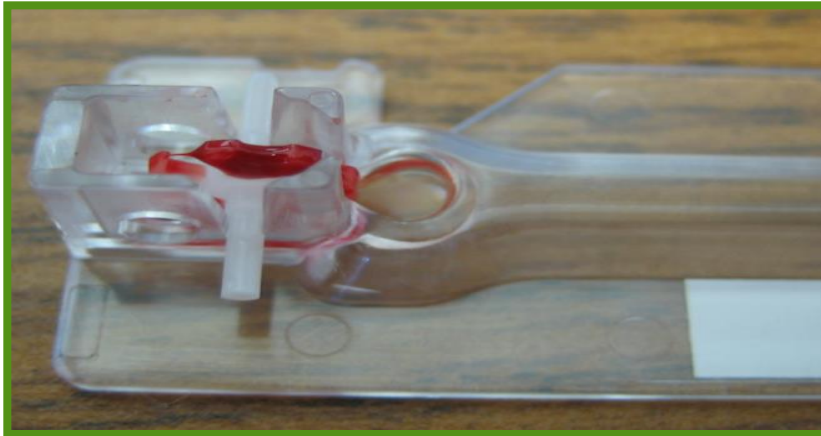


“Make things as simple as possible, but not simpler.”  
-Albert Einstein-

# POC PT/INR System Design Challenge

## Direct Micro-Mechanical Clot Detection

- Generates and picks up clot (plasma or whole blood)
- Simple timer
  - No algorithms monitoring a secondary reaction or changes in current
  - True PT - Testing time is patient's actual clotting time
- Not impacted by hemoglobin and hematocrit levels
- Affords excellent accuracy and precision (CV 2.5%) and linearity in high INR range



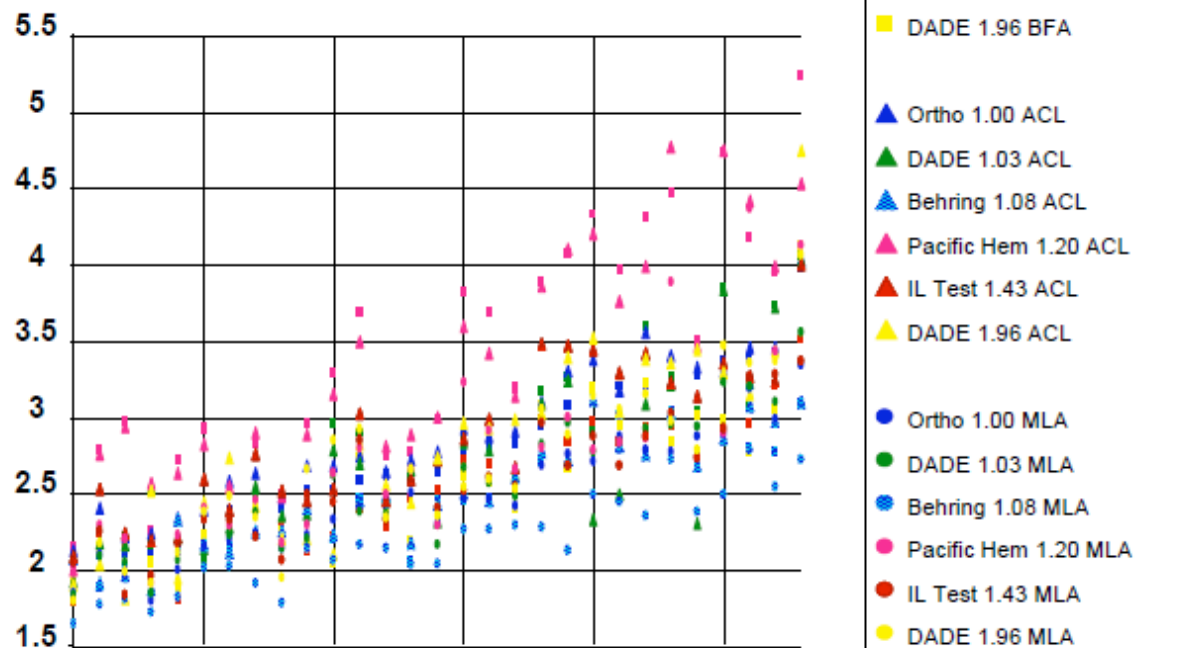
Test Strip with blood clot at top of micro wheel. Offers visual confirmation of clot formation (endpoint).



Close-up of micro wheel removed from a test strip.

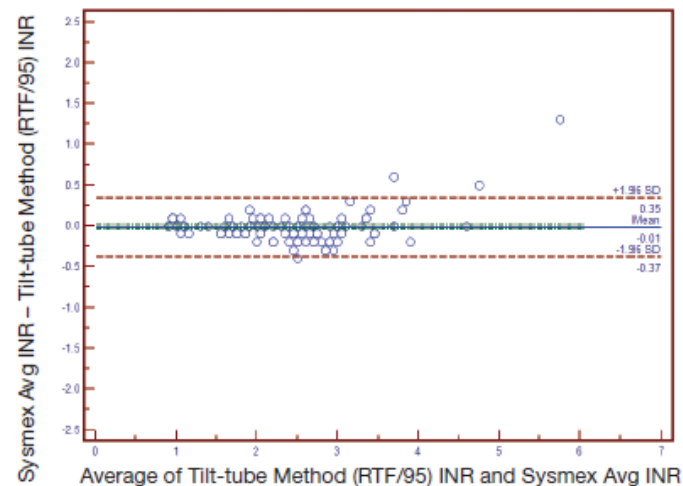
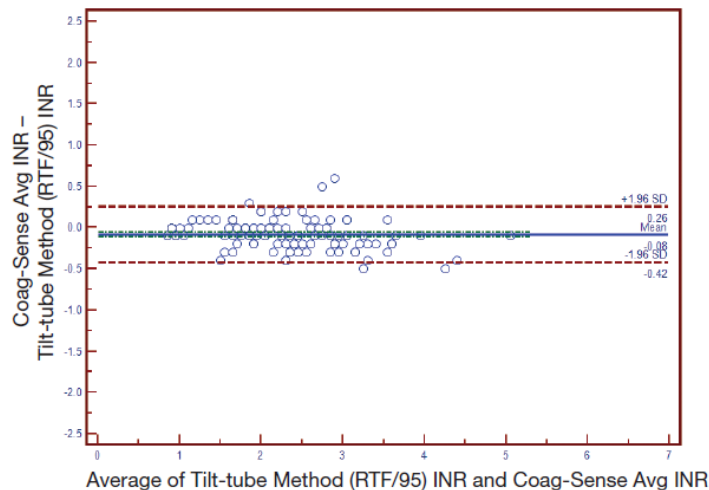
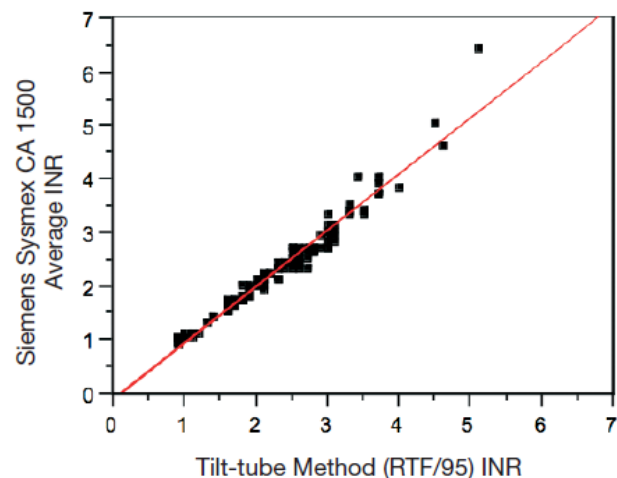
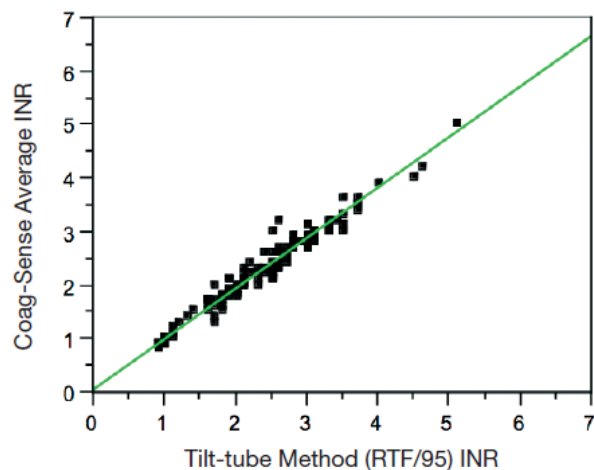
# The POC PT/INR System Benchmark Challenge

## Thromboplastin — Reagent Combinations: *Observed Variation in INR*



Jacobson

# The POC PT/INR System Benchmark Challenge

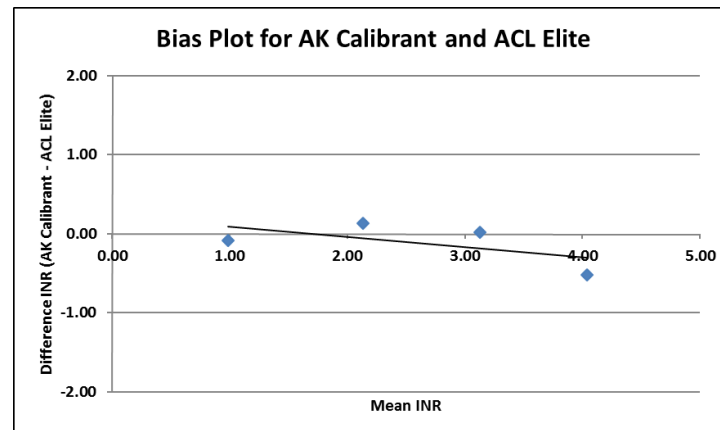
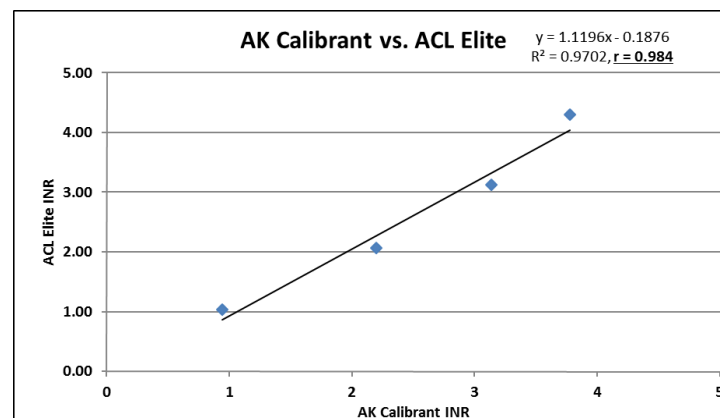
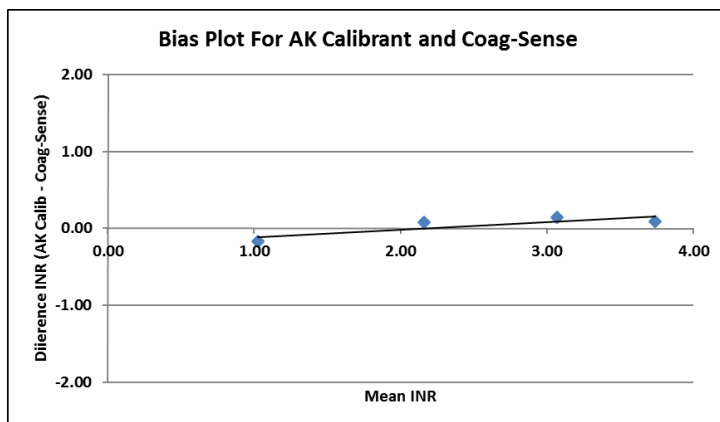
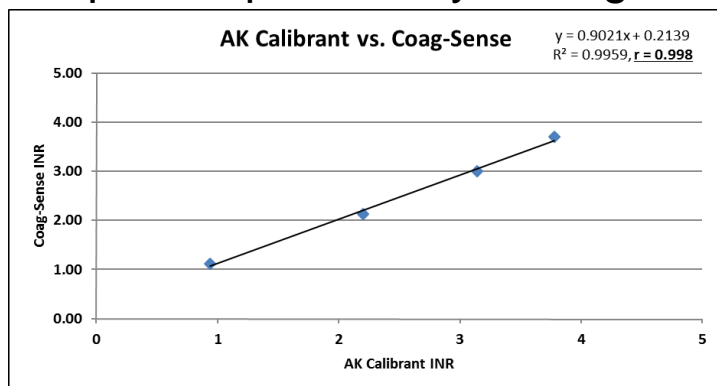




# The POC PT/INR System Benchmark Challenge

**Ability to run plasma controls and calibrants is key**

- Confirm system performance – *POC device is guilty until proven innocent*
- Participate in proficiency testing



# The Quality Control Testing Challenge

## The Importance of True Quality Control Testing

- Must verify performance of device and reagent
- Yet most POC PT/INR systems do neither
  - Leading On-Board “Controls” are not true functional tests and do little if anything to detect errors - or potential ones - or protect public as demonstrated by recent recalls
    - No substitute for testing actual thromboplastin reagent with real plasma sample
    - No whole blood control available yet so must be able to run plasma
  - Thromboplastin can be made robust and kept stable if individually pouched (moisture is enemy)
  - Confirming ability of device to properly detect clotting end-point is essential



# Human Factors

## POC Training

- Assign and train a super user at each site and use check list and sign off
- Changes in end user demographics (less RNs more MAs) increase training importance
- Sample acquisition not an issue as long as user understands that it is a timing assay
- Must demonstrate proficiency in performing an actual finger stick
- Quality of training more important than whether in-person or remote

## PST Training

- Patients are motivated
- PST service providers in general do a good job training patients or their care givers
- Skilled nurse trainers, quick reference guides and videos are most helpful



# Summary

- Detecting clot via secondary means can be challenging
- Must manage interfering substances
- If susceptible to hematocrit then require a hematocrit test
- CVs of >5% are problematic as monitoring patient over time
- Lab systems are NOT the gold standard
- Use WHO tilt-tube/reference preparation as gold standard
- Use actual thromboplastin and real plasma for QC – no contrived mixtures to simulate clot
- Participate in proficiency testing
- System must handle 10% bleach for BBP control
- Insist that each user practice test

**Thank You**

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**FDA PT/INR Public Meeting**  
**Manufacturer's Perspective on POC PT/INR**  
**March 18, 2016**

***Tracy Bush, Ph.D., DABCC, RAC***  
***Roche Diagnostics***



# Roche POC PT/INR Product Overview



## General technology and facts

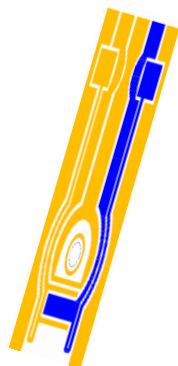
- CoaguChek® systems provide electrochemical measurement of clotting time with calculation of PT and INR following activation with human recombinant thromboplastin
  - Home use/ PST and professional setting
  - Over 1 million meters used worldwide
  - >250,000 CoaguChek XS PT test strips used **per day**

Product	Complaint rate
CoaguChek XS PT Test strip	3.4 ppm
CoaguChek XS Meter	0.008%
CoaguChek XS Plus/Pro Meters	0.06 %

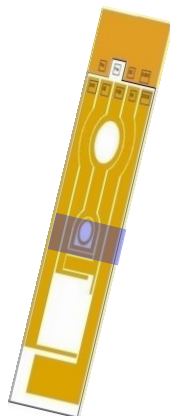


# Roche POC PT/INR Product Overview

## Controls: On-Board Quality Control (OBC)



- On-the-spot check of system integrity done with every PT/INR measurement
- Captures same erroneous conditions as traditional controls **PLUS**
  - Mechanical stress (bending, scratching, peeling)
  - Environmental extremes (temperature, humidity, light)



- Much more sensitive than traditional liquid controls
- Not intended as alternative concept to mimic liquid controls
- **Optional** liquid control is offered to help professional users fulfill obligations
- Quality concept includes other integrated system failsafes and interference testing



# Roche POC PT/INR Product Overview

## Measuring range: 0.8 – 8.0 INR

- Supported via method comparison and precision using natural samples.
- ACCP Guidelines (v.9) give Vitamin K treatment recommendations for patients with INRs between 4.5 and 10; and above 10.
- There is no gold standard (WHO IRP) available above 4.5
- CAP proficiency surveys do not include samples near 10
- Variation between lab-based reference methods increases with INR
  - 17% variation at 5.5 INR Source: CGL-C 2012 CAP survey

**Both** POC and lab-based methods have questionable performance at higher INR due to lack of a reference.

# Roche POC PT/INR Product Overview

## Acceptance Criteria : 510(k) clearance

- Roche POC PT/INR systems 510(k) cleared with data showing:
  - Equivalence to CoaguChek predicate
  - Comparison to lab-based reference method using these acceptance criteria:

INR level	Allowable Difference (90% of all results)	Samples meeting 30% or $\pm 0.5$	Samples meeting 20% or $\pm 0.5$
< 2.0	+/- 0.5 INR		
2.0 to < 4.5	+/- 30%	100%	>97.0%

- No other criteria were available
  - No POC PT/INR devices have been cleared with different acceptance criteria.
  - No FDA guidance documents stated different acceptance criteria
  - No outcome studies to establish medically relevant acceptance criteria

# Roche POC PT/INR Product Overview

## CLIA Waiver Acceptance Criteria

- CoaguChek XS and XS Plus achieved CLIA Waiver based on patient vs. technician studies (using POC device)
- Home Use/ PST devices can use same patient vs. technician study plan
- Professional Use devices must use CLIA Waiver Application process
  - Requires comparison to lab-based reference method
  - Accuracy criteria based on “performance limits for professional use”
  - FDA expects use of performance limits from the CLIA regulations\*
    - Designed for lab proficiency testing of non-waived methods
    - PT criteria are  $\pm 15\%$

CLIA waivers should be based on demonstration of equivalent accuracy between waived and non-waived operators, using the same method.

# Reasons for Variability : POC PT/INR vs. Lab Reference

## It's not just a POC problem



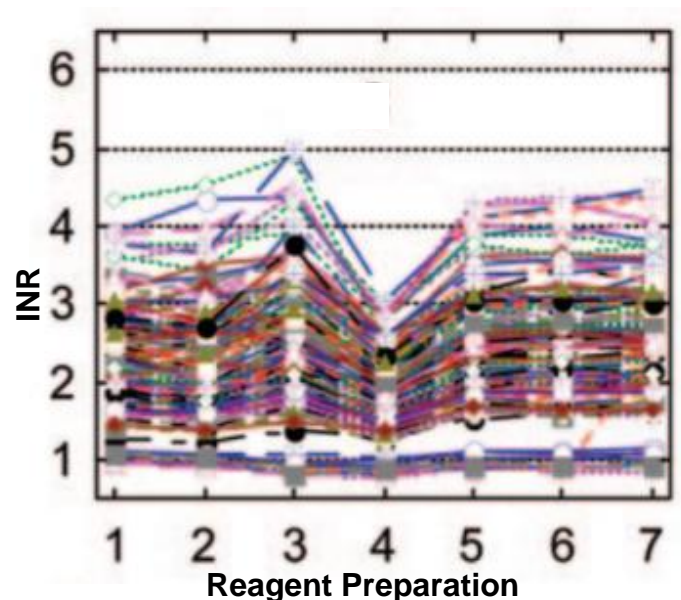
Variability exists between PT/INR results generated from

- Different reagents and device/reagent combinations
  - 3 WHO IRPs (recombinant human, rabbit, bovine)



- Different thromboplastin reagents
- Calibration of a POC device to a WHO IRP provides best fit to WHO gold standard, but not necessarily to other devices
- Even lab devices calibrated to the same IRP give different results

# Different lab methods give different PT/INR results



149 samples  
 Same analyzer  
 Same calibration  
 7 different reagents

Source: Horsti *Clin Chem* 51:3 (2005)

## ....Variability affects comparison to POC PT/INR

	Reagent A		Reagent B	
	Analyzer A	Analyzer B	Analyzer A	Analyzer B
Slope vs CoaguChek XS	1.03	1.13	1.44	1.11

It's not just a POC problem

Source: Roche internal data Sep 2014

# Reasons for Variability : POC PT/INR vs. Lab Reference

## It's not just a POC problem



Variability exists between PT/INR results generated from

- Different reagents and device/reagent combinations
- Different lots of reagent, with different ISI / calibrations
  - Labs often recalculate the calibration for each new lot of reagent
  - POC meters calibrations/ ISI are usually set by the manufacturer



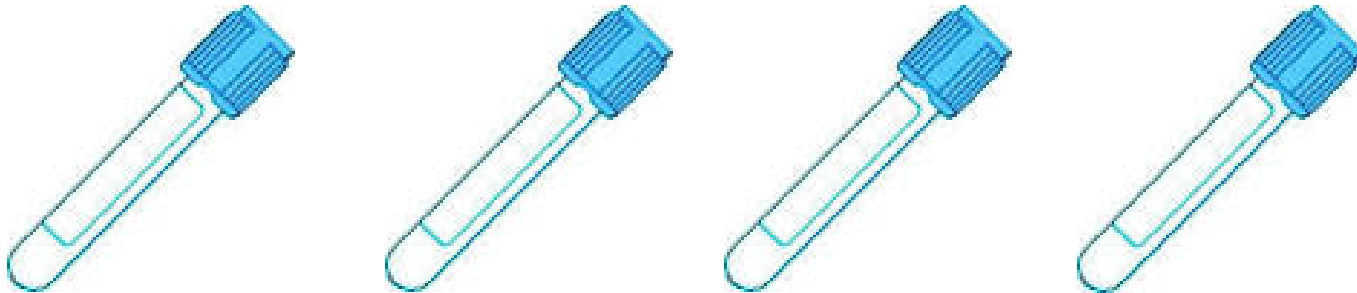
# Reasons for Variability : POC PT/INR vs. Lab Reference

## It's not just a POC problem

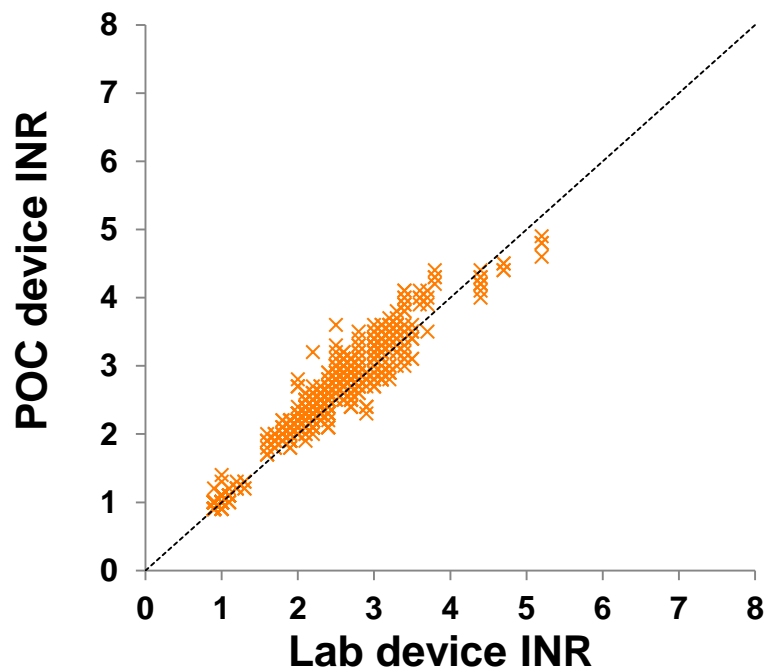


Variability exists between PT/INR results generated from

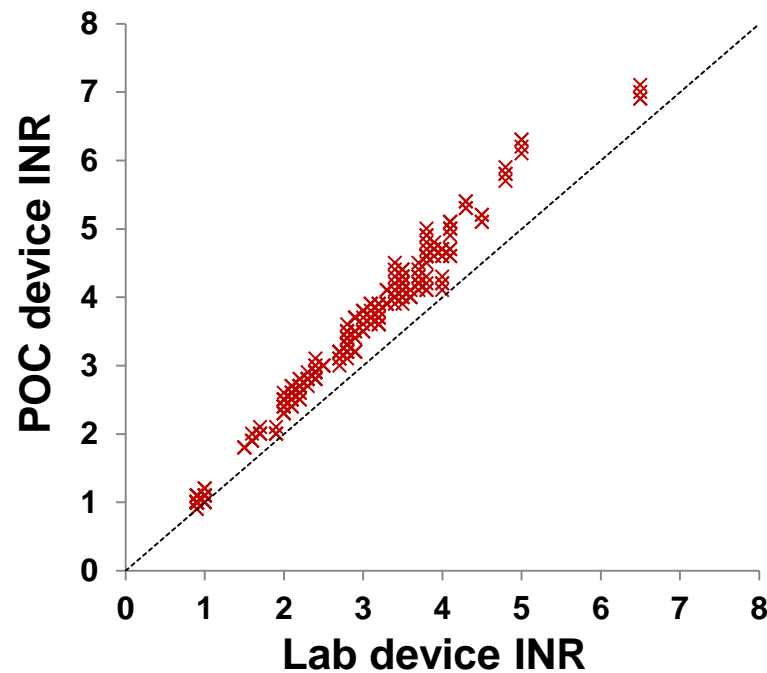
- Different reagents and device/reagent combinations
- Different lots of reagent, with different ISI / calibrations
- Different brands, and even lots, of blood collection tubes



# Different brands of blood collection tube give different method comparison results



**Using Brand X 3.2% citrate tubes**



**Using Brand Y 3.2 % citrate tubes**

Lab device testing performed on same device on same reagent lot, same day

Different samples collected with same protocol.



## Reasons for Variability : POC PT/INR vs. Lab Reference

**It's not just a POC problem**



Variability exists between PT/INR results generated from

- Different reagents and device/reagent combinations
- Different lots of reagent, with different ISI and calibrations
- Different brands, and even lots, of blood collection tubes

**Changing the POC PT/INR device accuracy criteria will not solve these issues.**

# **Recommendation: Manufacturers should help educate clinicians about PT/INR POC vs Lab Method comparisons**

- CAP emphasizes the need for POC PT/INR troubleshooting by trained individuals
- New POC devices must be verified against the lab method before being used in the facility –should be repeated often
- Raise awareness of reasons why the INRs from different methods are not equal
  - Know what reagent device combinations are being used
  - Know how recently the calibration happened
  - Investigate pre-analytic issues
    - sampling tubes
    - timing of POC vs lab draw
  - Investigate patient-specific issues like factor deficiency, concomitant drugs

**It's not just a POC problem**

# Summary



- Roche POC PT/INR systems provide safe and effective PT/INR testing
- Variability between POC and lab-based PT/INR methods is normal, and is not purely a POC problem
- CLIA Waivers should be based on comparisons of accuracy obtained by operators using the same method
- Manufacturers can assist with educating clinicians about the variability

***Doing now what patients need next***

# Session 4: Manufacturer Perspectives

## Q&A

Docket No. FDA-2015-N-4462



# Public Comment

**Docket No. FDA-2015-N-4462**



**April Bush**

**Facility Anticoagulation Program  
Manager at Wilmington VAMC**

**Docket No. FDA-2015-N-4462**



# Point of Care Testing (POCT) in the Outpatient Anticoagulation Clinic

April M. Bush, PharmD, CGP  
Facility Anticoagulation Program Manager



# Overview

- Background
- Pros/Cons of POCT for monitoring warfarin therapy
- POCT Practice Pearls
- Future Considerations

# Background

- Outpatient Anticoagulation Clinic
  - Clinical Pharmacy Specialist (CPS)
  - Medical Support Assistant (MSA)
- Face-to-Face Appointment
  - Initial (40 min)
  - Follow-up (20 min)
- Telephone Appointment
- Point of Care Testing Device
  - CoaguChek XS Plus



# Pros & Cons of Point of Care Testing (POCT)

## Pros

- Real time results
- Improved patient satisfaction
- Improved access of care
- Improved patient compliance with monitoring and appointments
- Improved clinic efficiency

## Cons

- Variability in patient response
- Range of Measurement of the device (0.8-8.0)
- Medication Interference
- Disease Interference
- Technique of user
- Cost

# Practice Pearls

- Ancillary Testing Operator Manual
- Policy, Procedures & Protocol
  - Inclusion criteria/Exclusion criteria
  - INR out of range
- Competency Assessments
  - Certification
    - Written exam, self-study and direct observation
  - Recertification (required yearly)
- Maintenance Log (required daily)
- Selection of Device
  - Interface with Electronic Medical Record (EMR)



# Practice Pearls Cont.

- Limit Certified Operators
- Adequate POC devices on-hand
- Quality Assurance
  - Quality control (external liquid quality control test)
  - Randomly will have patients have both POCT & Venipuncture
  - Participate in INR College of American Pathologists (CAP) survey

# Future Considerations

- Patient self-testing
  - Required to be enrolled into the AC clinic
  - Required to have face-to-face standardized educational program
    - Competency Assessment
  - Device is going to have be approved by our Lab
    - Pt must agree with on-going quality assurance monitoring
- New POCT Device
  - Built-in barcode reader





# Thank You!

April M. Bush, PharmD,. CGP  
Facility Anticoagulation Program Manager  
[April.Bush@va.gov](mailto:April.Bush@va.gov)

# **Jay Ronquillo, MD, MPH, MMSc, MEng**

## **National Center for Health Research**

**Docket No. FDA-2015-N-4462**





**Sidney M. Wolfe, MD**

**Founder, Senior Advisor**

**Public Citizen**

**Docket No. FDA-2015-N-4462**



FDA Workshop on Point of Care Prothrombin  
Time/International Normalized Ratio Devices  
for Monitoring Warfarin Therapy  
March 18, 2016

Testimony by Sidney M. Wolfe, MD  
Public Citizen's Health Research Group

I have no conflict of interest

# Two overarching problems highlighted by the INRatio/ROCKET AF case

- Inadequacy of the low FDA legal standard of substantial equivalence [510(k)] for devices needed to monitor life-threatening conditions.

**“(i) any differences in technological characteristics do not raise different questions of safety and effectiveness and (ii) information submitted demonstrates that the new device is as safe and effective as the predicate device.”**

- Dangerous failure of parties involved---CDRH, CDER, Rocket AF investigators, Janssen/Bayer, INRatio manufacturers---to promptly investigate, communicate serious device warnings to all other parties and take appropriate, necessary actions

14 months before ROCKET AF began, FDA (CDRH)  
October 2005 warning to INRatio's manufacturer

**“Our review indicates that your firm had information indicating that INRatio devices were generating clinically significant erroneous values. ... If the INR is too low, a patient will be prone to form blood clots or strokes. If the INR is too high, a patient will be prone to excessive bleeding. Therefore, both [erroneously] high and low test results have the potential to cause or contribute to a death or serious injury, because: they may result in erroneous [warfarin] dosing and thus improper control of coagulation”**

Food and Drug Administration. Inspections, compliance, enforcement, and criminal investigations: HemoSense Corporation. October 4, 2005.

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2005/ucm075594.htm>.

# FDA Cases of Serious Injuries with Faulty INRatio Devices (pre-ROCKET)

Event Date	INRatio INR	Lab INR	Treatment	Injury
03/04/05	1.8	8.0 (after Hosp’n*)	Increased warfarin (after 1.8 INR)	Hospitalized* 2 days later; 3 days after this, in hospital with spinal bleed and lower body paralysis 1
10/12/05 Three pts	1.7 1.9 1.5	2.6 4.8 3.3		Rectal bleeding and bruising Lab INRs measured < 1hour after INRatio
2/24/06	1.9	9.0 (next day)		Bruises and a swollen arm
3/1/06	1.3	6.0 in hospital	Hospitalized	Coughing blood and nosebleed
3/27/06	2.6	6.3		Lost vision in one eye for 5 minutes
4/4/06	1.6	8.0	Hospitalized	
From FDA Maude Reports				
5/18/06	2.4	>7.8		Vaginal and gum bleeding
7/6/06	1.2	20.9	Hospitalized	Nose and ear bleeding
4/29/05	2.8 2.8	4 days after 2 <sup>nd</sup> 2.8, 15.0	Warfarin after low readings, then hosp’n	<b>Death</b> after high reading in hosp. Dr. does not trust device but is incredulous as to what occurred

# 2007 study comparing INRatio with four other POC devices

- “Direct comparison of POCT results against the standard method using linear regression analysis suggested that correlation increased with increasing INR with all but the INRatio”
- “only the INRatio had more than 10% of results greater than 1.0 INR units difference”
- The Hemochron Junior Signature, ProTime and CoaguChek S demonstrated strong correlation with the laboratory method ( $R^2 > 0.94$ )...percentages of paired results within 0.5 INR units (81.5, 92.0 and 74.0%, respectively); the INRatio and TAS demonstrated 54.2 and 62.2%, respectively.

February 5, 2016 EMA report\* based on Janssen/Bayer analyses of ROCKET AF paired INRatio/lab INR: 6+ years after ROCKET AF was finished, 4+ years after Xarelto AF approval

- “the ROCKET AF trial was not designed to validate the performance of the POC device or to calibrate it against a Lab based INR.” (quote from Janssen/Bayer p. 36)
- “When analysing the MAH [company] data, it appears that 64 INR values were excluded in these analyses as the device INR were  $\geq 6.1$ .” (p. 26)
- “the proportion of measurements with a lower Device INR values compared with Lab INRs values are reduced from 34% to 29% according to the rapporteur’s calculation, **a number which still could be of some concern in relation for the possibilities of inappropriate dosing.**” (p. 28)
- “(273 out of 5766) of the measurements for Device INR were lower by two categories compared to the Lab INRs, **meaning the dose would have been increased or maintained when should have been decreased** (according to the INR categories)” (p. 28)

\* 2/10/16 EMA report on INRatio/ROCKET AF data (page of report after each quote above)

# Conclusions

- **Five parties---FDA CDER, FDA CDRH, Janssen/Bayer, ROCKET AF investigators and INRatio makers---were not responsibly or promptly communicating with each other more than 10 years ago, when serious problems with INRatio reliability were first known, but, unacceptably, neither shared nor seriously acted upon.**
- **FDA's CDER should continue its investigation of INRatio device failure to provide accurate readings, including but not limited to companies' exclusion from its analysis for the EMA of 64 ROCKET AF readings in which the INRatio INR reading was 6.1 or higher.**
- **The failure of FDA to require pre-market evidence of acceptable comparability of these POC (point of care) devices to standard lab determinations argues strongly for CDRH reclassification to require such premarket studies.**
- **CDRH should consider removing the INRatio device from the market**



## ***Final Words and Meeting Wrap-Up***

**Lea Carrington, MBA, MS, MT(ASCP)**

Division Director

Division of Immunology and Hematology Devices

OIR/CDRH/FDA

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